Country versus pharmaceutical company interests for hepatitis C treatment

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Abstract

Hepatitis C virus (HCV) is one of the leading causes of liver disease and is responsible for massive health and economic burden worldwide. The disease is asymptomatic in its early stages, but it can progress over time to fatal end-stage liver disease. Thus, the majority of individuals infected with HCV are unaware of their chronic condition. Recent treatment options for HCV can completely cure the infection but are costly. We developed a game model between a pharmaceutical company (PC) and a country striving to maximize its citizens' utility. First, the PC determines the price of HCV treatment; then, the country responds with corresponding screening and treatment strategies. We employed an analytical framework to calculate the utility of the players for each selected strategy. Calibrated to detailed HCV data from Israel, we found that the PC will gain higher revenue by offering a quantity discount rather than using standard fixed pricing per treatment, by indirectly forcing the country to conduct more screening than it desired. By contrast, risk-sharing agreements, in which the country pays only for successful treatments are beneficial for the country. Our findings underscore that policy makers worldwide should prudently consider recent offers by PCs to increase screening either directly, via covering HCV screening, or indirectly, by providing discounts following a predetermined volume of sales. More broadly, our approach is applicable in other healthcare settings where screening is essential to determine treatment strategies.

Keywords Game theory · Hepatitis C virus · Healthcare management · Cost-effectiveness analysis · HCV screening · Risk-sharing agreements

Highlights

- Hepatitis C virus (HCV) is one of the leading causes of liver disease and is responsible for massive health and economic burden worldwide.
- Recent treatment options for HCV can completely cure the infection but are costly. In several developed countries, HCV treatment is provided for free by the pharmaceutical companies (PC) if a certain quantity of treatment courses is purchased. In other countries, PC funds screening to identify more HCV-infected individuals. Given the high burden of HCV, both strategies might be perceived as ethical and vital, as they benefit the PC and society at large.
- We developed a game model between a pharmaceutical company (PC) and a country striving to maximize its citizens' utility and employed an analytical framework to calculate the utility of the players for each selected strategy.
- Calibrated to detailed HCV data from Israel, we show that due to the slow progression of HCV these strategies are suboptimal to the country. By contrast, risk-sharing agreements, in which the country pays only for successful treatments are beneficial for the country.
- More broadly, our approach provides a general framework that can be applied to many other healthcare settings where screening is essential to determine treatment strategies.

1 Introduction

Hepatitis C virus (HCV) is one of the leading causes of liver disease, causing massive public health and economic burden worldwide. The virus leads to chronic illness and increases the risk of liver cirrhosis, hepatocellular carcinoma, liver failure, and death. Recently, the World Health Organization (WHO) suggested that over 70 million people are chronically infected with HCV and that each year HCV-related

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complications account for approximately 400,000 incidents [1, 2]. Disease prevalence varies widely between continents, ranging from 1.3% in the Americas to 2.9% in Africa [2–4], and poses a substantial burden to both developing and developed countries. In the US, it is estimated that 3.5 million people are chronically infected with HCV [5]. Moreover, each year the disease is responsible for the deaths of 20,000 individuals in the US, more than any other infectious disease prior to the COVID-19 pandemic [5].

Disease complications are, indeed, fatal, but only a small subset of individuals infected with HCV will develop end-stage liver disease. After HCV enters the blood, 15% to 45% of patients clear the virus spontaneously within six months [6, 7]. For those in whom HCV RNA persists in their blood for more than six months, the infection will progress into a chronic condition. The infection can be determined by screening individuals using a simple and inexpensive antibody test [8]. Although hidden inflammation progresses in the liver for those infected, most individuals are unaware of their chronic condition [9]. Inflammation progression is commonly estimated by the fibrosis progression rate of the liver and is expressed by a five-degree classification system ranging from stage F0 (no fibrosis) to cirrhosis at stage F4 [10]. Advanced checkup tests can be used to determine the fibrosis stage, but are more expensive than just determining infection [11]. A chronically infected individual may carry the virus for more than 30 years before developing any clinical symptoms; thus, only 10–20% of infections progress to end-stage liver disease [12].

A sharp decline in HCV infection has recently been observed due to advances in hygiene practices which reduced transmission through direct blood-to-blood contact as well as due to recent breakthroughs in HCV treatments. Thus, with the exception of injecting drug users that are at elevated risk to contract HCV due to the sharing of contaminated injecting equipment [13–15], the prevalence of HCV in the general population gradually declines. These treatments, which have been approved by the US FDA [16] and the European Medicines Agency since 2014, show low side effects and excellent efficacy in clearing the virus and halting liver deterioration. Although clinical trials have demonstrated high efficacy of the treatments, the efficacy declines with disease progression. For example, Sofosbuvir showed efficacy of 0.98, 0.98, 0.92, and 0.79 in stages F0, F1, F2, and F3, respectively [17]. Due to the dramatic decline in HCV disease, the World Health Assembly endorsed a Global Health Sector Strategy in 2016, calling for the elimination of HCV as a public health threat by 2030 by improving screening and treatment policies [18, 19].

The main barrier to prompt elimination of HCV is the high price of treatment, which is unaffordable globally [20]. Pharmaceutical companies have developed and adapted differential pricing strategies to increase revenue in each country [21]. For example, while the US government paid $84,000 per course of Sofosbuvir, the price in Spain was as low as $25,000 [22]. Due to the high price of treatment, numerous studies have evaluated the cost-effectiveness of different screening policies that are specific to each country and to the individual's stage of infection [17, 23–29]. These health economic studies aim to balance the declining efficacy of treatment with disease progression and the understanding that for most people, natural death will occur before reaching HCV stage F4. However, although these studies underscored that the worldwide policy to combat HCV must be revised to reduce mortality, they did not optimize the frequency of checkups, which are essential to determine the fibrosis stage. Given that a decision to treat is based on the most up-to-date checkup test result regarding the fibrosis stage, rather than the actual stage itself, optimizing the frequency of checkups should be explicitly integrated into the cost-effectiveness evaluations.

The high proportion of undiagnosed individuals, the slow progression of the disease and the technological ability to diagnose and identify the HCV fibrosis stage provide a rich and broad level of strategies for policy makers to reduce the burden of HCV. These opportunities result in nontrivial pricing mechanisms for HCV treatment. Recently, various PCs have begun to provide discounts after a predetermined volume of sales. Such approaches are now widely used in Australia, France, Canada, and New Zealand [30, 31]. In some countries, PCs share the risk of treatment outcome and reimburse the country if treatment is unsuccessful [32–34], while in other countries, they fund screening to identify more HCV-infected individuals [35, 36]. Given the high burden of HCV, these strategies might be perceived as ethical and vital, as they benefit not only the PC but also society at large.

Game theory provides an analytical framework to analyze the outcome of the conflict between rational decision-makers [37]. Several recent studies integrated game models with disease transmission models to explore the dynamics between manufacturers and decision-makers [38–46]. Chick et al. [41] explored the procurement of influenza vaccines in settings where production yield is uncertain and an information asymmetry exists between the manufacturer and policy makers. Özaltin et al. [40] optimized the design of a flu shot by accounting for its effect on the societal benefit by determining coverage and time availability. Using a sequential game model, Chick et al. [47] showed that production risks taken by the influenza vaccine manufacturer lead to an insufficient supply of the vaccine. The authors suggested that a global social optimum cannot be fully attained by changing the vaccine price and demonstrated that a variant of the cost-sharing contract can align incentives to achieve a social optimum. The authors further showed that due to the nonlinear health benefit of influenza vaccination, nonlinear pricing can serve as a valuable coordination mechanism. Only two studies have considered a game model for HCV

policy determination. The first focuses on a unique setting of a compulsory license agreement in developing countries [38], while the latter considers different treatment cost functions to optimize the budget of a social planner in a theoretical game [48].

Therefore, we developed a game-theoretic model to assess the price of HCV treatment in consideration of the corresponding screening, checkup and treatment strategies. We employed an analytical framework calibrated to detailed HCV data from Israel to calculate the utility of the players for each strategy chosen. This study is the first to optimize treatment policy and determine comprehensive guidelines to combat HCV by considering simultaneously both screening campaigns to identify individuals with HCV infection and checkup rates for those infected. Our model provides a rational explanation for the current strategies offered by PCs to fund screening or to provide a substantial discount after a predetermined volume of sales, which results in a suboptimal outcome for the country. In addition, we present applicable mechanisms for the country to mitigate this outcome.

2 The basic model

2.1 Game model

We consider a game model composed of two players: a Pharmaceutical Company (PC) striving to maximize its revenue, and a country[1] endeavoring to maximize the social welfare of its citizens. The sequence of the game starts with the PC announcing a fixed price of treatment, $p \geq 0$, which represents the price of a full-course treatment for an individual infected with HCV. Then, the country determines which subpopulations will receive the treatment based on certain criteria. As common in worldwide guidelines [49, 50], these criteria are based on the individual's age[2] and the stage of fibrosis (i.e., disease progression). The actual stage of fibrosis at each time point is unknown but can be frequently determined by checkup tests. Thus, for each individual, we distinguish between their actual fibrosis stage (denoted by f) and their presumed stage (namely, their last diagnosis, denoted by d), which is based on the most recent checkup test results. We define $y = (y_0, y_1, y_2, y_3)$ as the vector of checkup rates determined by the country, such that $y_d \geq 0$ represents the checkup rate for individuals diagnosed with fibrosis stage d. Similarly, we define $x = (x_0, x_1, x_2, x_3, x_4)$ as

a binary vector describing the country's decision of whether to treat an individual at presumed fibrosis stage d. Thus, the PC's strategy is to determine the price of treatment p, and the country's strategy is to determine both the treatment criteria x and the checkup rates y[3]. The PC's expected present-value utility is given by:

$$U^{PC}(x, y) = p \cdot N_T(x, y), \tag{2.1}$$

where N_T is the expected discounted[4] number of treated individuals.

In line with standard cost-effectiveness studies [51], the expected utility for the country comprises the overall health benefits to the population translated into financial outcomes, reduced by the overall direct and indirect costs of the disease. The health benefits comprise the overall life-years gained by the population, translated into economic costs. c_H represents the economic losses attributable to HCV that arise upon reaching an end-stage liver complication. These losses may include hospitalizations and liver transplantations. Additionally, we consider the costs of checkups, c_C, and treatment, p. Thus, the expected utility for the country is given by:

$$U^{COUNTRY}(x, y) = v \cdot QALY(x, y) - \{c_H N_H(x, y) + p N_T(x, y) + c_C N_C(x, y)\}, \tag{2.2}$$

where v is the financial value equivalent to one healthy year, multiplied by the total discounted quality-adjusted life-years earned by the entire population,[5] $QALY$. $N_H(x, y)$ is the expected discounted number of individuals hospitalized due to HCV complications and $N_C(x, y)$ is the expected discounted number of individuals tested to determine their fibrosis stage (an analytical formulation and solution for these values based on our HCV dynamic disease transmission model is presented in Appendix 5).

Proposition *There exists a subgame perfect Nash equilibrium* , $(p^*, (x(p), y(p)))$.

Proof As previously proven by Selten, at least one subgame perfect Nash equilibrium $(p^*, (x(p), y(p)))$ exists for any finite game [52], and can be determined through backward induction, (see also, for example, [37, 53, 54]). For each treatment price, p, set by the PC, the country decides on its

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[1] Represented by its government, a healthcare provider or a formal policy maker.

[2] To improve clarity and readability, the presented model equations do not account for age stratifications. An age-structured model is presented in the Appendices and is fully considered in our simulations.

[3] x and y are both fixed over time, as the country considers all individuals in an equal manner, regardless of their time of treatment.

[4] In such agreements, the treatment price remains fixed. Thus, the number of treated individuals is discounted, in accordance with standard economic evaluations. The financial discounting is further detailed in Appendix 5.

[5] For generality, we refer to the infected and uninfected population. If transmission of HCV is assumed to be negligible, only those infected with HCV are considered.

Fig. 1 Model of HCV disease progression with treatment. The model consists of two main partitions – untreated states (I) and treated states (T). In the untreated states, each node represents a transient state defined by the actual disease fibrosis stage and diagnosed stage (f, d). In the treated states, nodes are divided into two groups: susceptible following treatment (ST) representing individuals for whom treatment was effective, and infected following treatment (IT), representing individuals for whom treatment was not effective or individuals that were effectively treated but got re-infected. Each node represents a transient state defined as the actual disease fibrosis stage (f). If treatment is successful, f defines the last fibrosis stage before treatment for tracking. The untreated states can transition to two absorbing states (m), representing non-HCV and HCV deaths, respectively. Similarly, the treated states can transition to two absorbing states (m), representing non-HCV and HCV deaths. The gray circles represent the undiagnosed states (d). The orange circles represent the diagnosed states. The arrows from each state depict transitions to other states
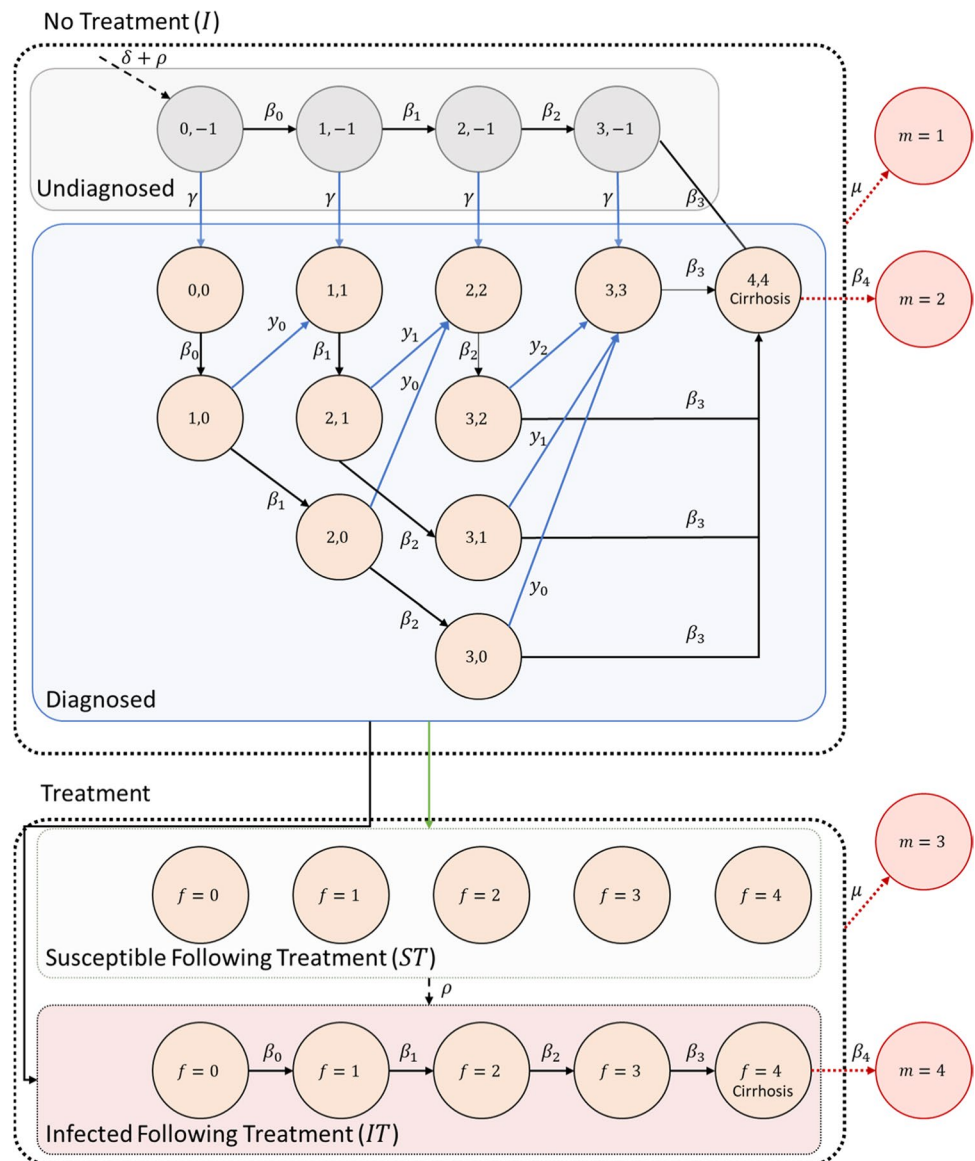
best-response policy, defined by the vectors x and y. The optimal policies were those that maximized the country's utility in response to each price. Since the PC acts first, the equilibrium is determined by the price of treatment that maximizes the PC's utility, considering the country's best-response policy.■

2.2 HCV Disease transmission and progression model

2.2.1 General population

In this section, we employed a dynamic model to describe the progression of HCV over time in the general population, i.e., disregarding injecting drug users (IDU) (Fig. 1). At each time t, individuals are classified into states,

$I_{f,d}(t)$, based on two characteristics[6]: f, their actual stage of fibrosis $f \in \{0, 1, 2, 3, 4\}$, and d, their diagnosed stage $d \in \{-1, 0, 1, 2, 3, 4\}$ observed in their most recent checkup test. Individuals in states $I_{*,d=-1}(t)$ are infected but have not been diagnosed with the disease. Misdiagnosis of fibrosis tests for determining the fibrosis stage is considerably low [55]; thus, we assumed a complete accuracy of checkup tests, indicating that $f \geq d$. End-stage cirrhosis is symptomatic; hence, the actual fibrosis stage is known at stage F4 (i.e., $f = 4 \rightarrow d = 4$). Taken together, the population in

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[6] To improve clarity and readability, the following model equations do not account for age and gender stratifications. A gender and age-structured model is presented in the Appendices and is fully considered in our numeric simulations.

the model is stratified into 15 states, and a transition from one state to another occurs as a result of natural disease deterioration or a change observed following a checkup test (Fig. 1).

Individuals are born at rate $\epsilon(t)$ and can be either susceptible to HCV or infected with HCV due to mother-to-child transmission at rate[7] δ [56]. We denote the susceptible population – individuals who might become infected in the future with HCV at time t as $S(t)$. We also denote the overall population at time t as $\mathcal{N}(t)$, and the population infected with HCV is $\sum_{i \in f, f \geq d} \sum_{j \in d} I_{i,j}(t)$, that is, the sum of all individuals in these 15 states. Newly-infected individuals enter state $I_{f=0,d=-1}(t)$, where the disease is in its earliest stage of fibrosis and individuals are unaware of their infection. Individuals transition out of this state due to deterioration of their fibrosis stage, HCV diagnosis from general screening, or natural death at rates β_f, γ and μ, respectively. Accordingly, the changes in the number of undiagnosed infected individuals in a short time interval Δt is:

$$I_{0,-1}(t+\Delta t) - I_{0,-1}(t) = \epsilon(t) \cdot \delta \cdot \mathcal{N}(t) + \lambda(t) \cdot S(t) - (\beta_0 + \gamma + \mu)I_{0,-1}(t).$$
(2.3)

The virus is transmitted as a result of contaminated blood via medical procedures at rate ρ. Thus, the rate at which individuals are infected with HCV at time t, that is the force of infection, is given by:

$$\lambda(t) = \sum_{i \in f, f \geq d} \sum_{j \in d} \rho \cdot I_{i,j}(t)$$

The country determines whether to treat infected individuals based on their presumed fibrosis stage. Equation 2.4 describes all the states in which the country is aware of the actual fibrosis stage of the patient, i.e. when $d = f$. Individuals enter these states only when their fibrosis stage is not treated per the country's policy, at rates y_i, $i \in \{-1, 0, 1, ..d-1\}$, the checkup rate at each diagnosed state i. For consistency, we define y_{-1} as the common HCV diagnosis rate γ [57]. Transition from these states to others at rates β_f and μ results from progression to the next stage of disease or from non-HCV death, respectively.

$$I_{f,d}(t+\Delta t) - I_{f,d}(t) = (1 - x_f)\left(\sum_{j=-1}^{d-1} y_j I_{f,j}(t)\right) - (\beta_f + \mu)I_{f,d}(t), \forall d = f \quad (2.4)$$

Equation 2.5 describes all other I states (where $d < f$). Individuals enter these states at rate β_{f-1} from a previous

stage of the disease, $f - 1$. Transition from these states to others at rates β_f, y_d and μ results from progression to the next stage of the disease, checkup, or non-HCV death, respectively.

$$I_{f,d}(t+\Delta t) - I_{f,d}(t) = \beta_{f-1}I_{f-1,d}(t) - (\beta_f + y_d + \mu)I_{f,d}(t) \; \forall d < f$$
(2.5)

The treated population is divided into two groups: susceptible following treatment (ST) representing individuals for whom treatment was effective, and infected following treatment (IT), representing individuals for whom treatment was not effective or individuals that were effectively treated but got re-infected. We assume that when the treatment policy starts at time $t = t_c$, individuals who follow the criteria immediately become treated. From time $t > t_c$, those who meet the criteria transition to the treated states at the country's chosen checkup rate. Let θ_f represent the efficacy of the treatment when provided at stage f. An individual in stage f can be diagnosed at rates y_i, $i \in \{-1, 0, 1, ..., f-1\}$; then, when the fibrosis stage is treated by policy ($x_f = 1$), the individual transitions to ST_f with probability θ_f, meaning the treatment was efficient. Alternatively, the individual transitions to IT_f if the treatment was inefficient. Conservatively and consistent with observations from clinical trials, retreatment following ineffective treatment is not considered. Transition from state ST_f can occur at rates ρ and μ because of HCV reinfection due to contaminated blood in a medical procedure or non-HCV death, respectively. We track the last fibrosis stage f, even if treatment was successful as the liver condition remains unchanged due to the very slow regression of fibrosis [58]. Transition from state IT_f can occur at rates β_f and μ due to progression to the next stage of the disease and non-HCV death, respectively.

$$ST_f(t+\Delta t) - ST_f(t) = \left(\sum_{k=0}^{3} x_k \theta_k \left(I_{k,k}(t) + \sum_{j=-1}^{k-1} y_j I_{k,j}(t)\right)\right) - ST_f(t)(\mu + \lambda(t))$$
(2.6)

$$IT_f(t+\Delta t) - IT_f(t) = x_f(1 - \theta_f)\left(I_{f,f}(t) + \sum_{j=-1}^{f-1} y_j I_{f,j}(t)\right)$$
$$+ ST_f \cdot \lambda(t) + \mathbb{1}_{f>0} \cdot \beta_{f-1} \cdot IT_{f-1}(t) - IT_f(t)(\beta_f + \mu),$$
(2.7)

where $\mathbb{1}_{f>0}$ is an indicator function taking a value one for all $f>0$ and zero otherwise. The initial conditions are given by $l_{f,d}$, representing the initial number of infected individuals at time $t = t_c^-$, that is, just before the treatment policy is applied in each state. Assuming that individuals are not yet treated at time $t = t_c^-$, the number of individuals at each state can be represented by:

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[7] In the age and gender structure model (Appendix 1), this rate is determined based on the birth rate multiplied by the probability of transmission, and is proportional to the number of females in the specific fertility age-group.
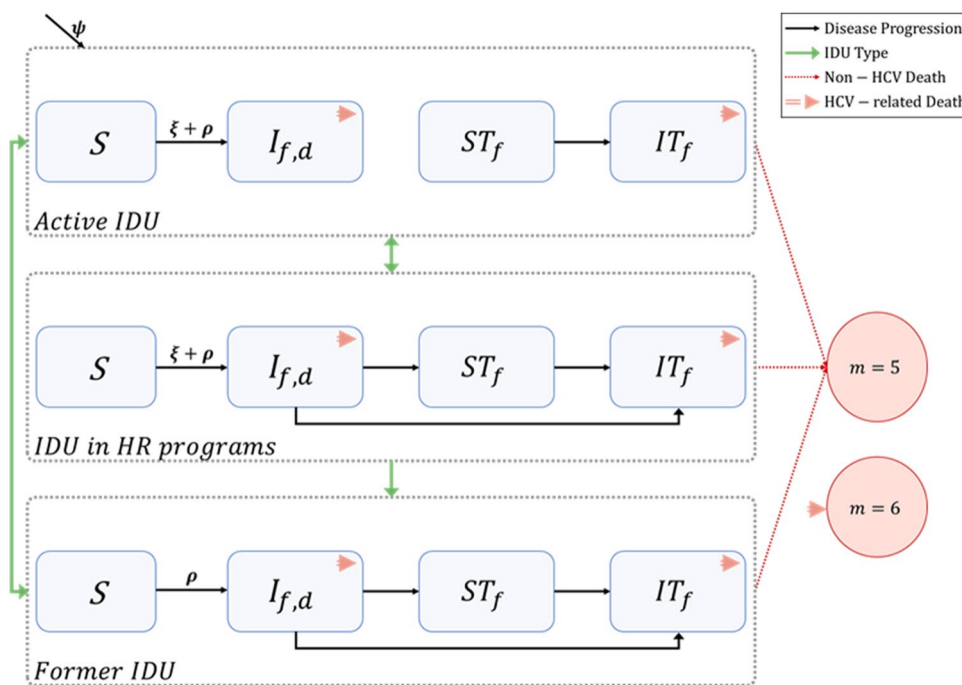
Fig. 2 Model of HCV transmission and progression among injecting drug users. The model consists of three main groups based on IDU status: 1) active IDU, 2) IDU in HR and 3) former-IDU. The model follows all injecting drug users as they transition between four sub-groups according to their disease status: 1) susceptible (S), 2) infected (I), 3) susceptible following treatment (ST) and 4) infected following treatment (IT). Newly active IDUs enter the model at rate ψ. Sus-ceptible individuals can become infected by contaminated blood via shared-drug use at rate ξ or via medical procedures at rate ρ. All sub-groups can transition to the absorbing state ($m = 5$), representing non-HCV death. States written with a double-compound orange arrow on the top right can transition to the absorbing state ($m = 6$), representing HCV death. The arrows from each state depict transitions to other states

$$
\begin{aligned}
S\left(t = t_c^-\right) &= \mathcal{N}(t) - \sum_{i \in f, f \geq d} \sum_{j \in d} I_{i,j}\left(t = t_c^-\right) \\
I_{f,d}\left(t = t_c^-\right) &= l_{f,d}, \quad \forall f = 0, \ldots, 4, d = -1, \ldots, 4 \\
ST_f\left(t = t_c^-\right) &= 0, \quad f \in \{-1, 0, 1, 2, 3, 4\} \\
IT_f\left(t = t_c^-\right) &= 0, \quad f \in \{-1, 0, 1, 2, 3, 4\}
\end{aligned}
\tag{2.8}
$$

Overall, the general population model with treatment includes 25 transient states (Fig. 1): 15 states describe HCV progression without treatment, five states describe HCV progression following an ineffective treatment, and five states describe successful treatment. Additionally, the model includes four absorbing states ($m\epsilon\{1, 2, 3, 4\}$) to explicitly distinguish between 1) non-HCV-related death in the non-treated population, 2) HCV-related death in the nontreated population, 3) non-HCV-related death in the treated population, and 4) HCV-related death in the treated population, where β_4 is the mortality rate from HCV.

2.2.2 Injecting drug users

We extend the model to explicitly include transmission dynamics among injecting drug users (IDU) (Fig. 2, detailed presentation of model equations is presented in Appendix 2).

In accordance with previous models [59–62], we stratify the IDU population into three mutually exclusive groups based on IDU status: 1) active IDU, 2) IDU in harm reduction (HR), and, 3) former-IDU. Active IDU refers to all individuals currently involved in intravenous drug use who are not enrolled in HR programs. When an IDU joins an HR program (for example, needle exchange and opioid replacement therapies [63]), the individual transitions to the IDU in HR group. Once the IDU completely ceases drug injection, the individual is classified as a former-IDU. Individuals transition between the IDU groups by means of drug rehabilitation or drug re-addiction, which may occur with or without HR. Thus, with the exception of a direct transition from former-IDU to IDU in HR, individuals may transition between all three groups multiple times throughout their lifetime (Fig. 2).

In accordance with the basic model, newly-active IDUs enter the active IDU group at rate $\psi_{i,s}$, where they can either be susceptible to HCV S^{Active}, infected with HCV I^{Active}, susceptible following treatment ST^{Active}, or infected following treatment IT^{Active}. For those infected with HCV, the disease progresses as described in Sect. 2.2.1; thus, the I^{Active} sub-group includes 15 transient states that explicitly track the

actual fibrosis stage (denoted by f) and presumed stage (denoted by d), i.e., $I_{f,d}^{Active}$. Similar to the general model, as treatment will not be offered again after reinfection, the ST^{Active} and IT^{Active} subgroups include five states each to explicitly track the five possible stages of fibrosis, i.e., IT_f^{Active} and ST_f^{Active}. As previously suggested [59, 64], and due to the considerable risk of reinfection [65], treatment is not offered to active IDUs. Nonetheless, individuals in the active IDU group may have already received treatment while in the IDU in HR group or the former-IDU group.

Upon joining HR programs, IDUs transition from the active IDU group into the equivalent state of the IDU in HR group (e.g., $I_{f=3,d=2}^{Active} \rightarrow I_{f=3,d=2}^{HR}$). Based on the country's decision of whether to treat an individual at presumed fibrosis stage d, eligible individuals transition to the matching state based on the outcome of treatment. Specifically, if the treatment is effective, individuals transition to a susceptible following treatment state ST. Recall that although the virus is cleared, the liver condition remains unchanged due to the very slow regression of fibrosis [58]; thus, individuals transition with an identical fibrosis stage (e.g., $I_{f=3,d=2}^{HR} \rightarrow ST_{f=3}^{HR}$). Likewise, if the treatment is ineffective, individuals transition to an infected following treatment state IT with an identical fibrosis stage (e.g., $I_{f=3,d=2}^{HR} \rightarrow IT_{f=3}^{HR}$). As reinfection is possible upon exposure to contaminated blood, susceptible individuals who were previously treated may transition to the infected IT state (i.e., $ST_f^{HR} \rightarrow IT_f^{HR}$).

Transitioning from the former-IDU group follows the same logic as that for the HR group with one exception. As former-IDUs do not inject drugs, they may transition to the infected groups (I^{Former} and IT^{Former}) only due to contaminated blood transfusion via a medical procedure. As long as former-IDUs do not become re-addicted and transition to the active IDU group, they do not contribute to the transmission caused by the shared-needle exchange.

In addition to blood transfusion due to medical procedures, IDUs may become infected with HCV via contaminated needles. Inspired by Kaplan's notion of needle circulation from the moment of its introduction into a population of IDUs [66, 67], we developed a nonlinear framework to model the force of infection due to needle exchange (Appendix 3). This framework explicitly evaluates the individual's risk of becoming infected with HCV as a function of the number of IDUs that previously used the needle. This needle-sharing procedure reveals a strong concave effect on the transmission following treatment (Appendix Fig. 8). The force of infection $\lambda^u(t)$ in IDUs at group u is:

$$\lambda^u(t) = \mathbb{1}_{u \in \{IDU, HR\}} \cdot \xi(t) + \rho \cdot \sum_{i \in f, f \geq d} \sum_{j \in d} I_{i,j}(t), \quad (2.9)$$

where $\xi(t)$ is the rate of infection due to needle-sharing and ρ is the rate due to contaminated blood via medical procedures.

3 Model extensions

In this section, we present several practical extensions. For each extension, we first present the problem description, and briefly describe the modifications from the basic model and the evaluations of the results at equilibrium. For reproducibility, the detailed model, the analytical solutions for each extension, and the code for the simulations are available on GitHub [68].

3.1 Extension 1 – One-time screening campaign funded by the country

We examine the effect of population screening that is paid by the country on the game's outcomes. In this extension, the PC determines the treatment price. Afterward, the country simultaneously determines a one-time screening policy, relating to the number of individuals screened at time $t = t_c$, as well as the check-up and treatment policy. This modification affects: 1) the initial number of individuals in each state, as screened individuals may transition to one of the diagnosed states, and 2) the country's utility function to account for the screening costs paid by the country. Given that a diagnosed individual is not screened again, we evaluate the expected number of identified HCV-infected individuals $E(X)$ using a hypergeometric process, $X \sim HG$ (M, D, s). A "success" indicates a newly diagnosed individual upon screening of s individuals in the undiagnosed population (M) containing D HCV-infected individuals. The campaign leads to an expected increase of $s \cdot \frac{D}{M}$ individuals in the diagnosed population, according to the proportion of each fibrosis stage. The screening cost, $C(s)$, is a function of s, the number of individuals tested for HCV. In practice, as s increases, it becomes more difficult to locate and convince an additional individual to undergo screening. Following the same logic, locating the first individual is relatively easy, and the cost is based primarily on testing. Thus, we demand $C(0) = 0$, $\frac{dC(s)}{ds} \geq 0$, $\frac{d^2C(s)}{ds^2} > 0$ and $\frac{dC(s=0^+)}{ds} \geq c_E$), where c_E is the fixed cost for a single HCV examination (i.e., screening).

3.2 Extension 2 – Pricing mechanisms

In this extension, we independently examine three pricing mechanisms recently observed in several developed countries. The first involves PC funding of screening, i.e., we subtract $C(s)$ from the utility function of the PC instead of the country's. The second considers the PC sharing the

Table 1 Parameter values used in the model

Symbol	Parameter	Values considered	Data source
$\beta_{f,i,s}$	Annual disease progression rate per fibrosis stage f, age group i and gender s		[71]
$\mu_{i,s}^{u}$	Annual death rate per age group i, gender s and IDU type u		Israeli Central Bureau of Statistics, [59]
ζ_{jk}	Annual rate of progression between IDU state j to IDU state k, where $j, k \in \{IDU, HR, Former\}$		[59]
θ_f	Efficacy of treatment per stage	[0.98, 0.98, 0.92, 0.79]	[17]
γ	Spontaneous annual screening rate before a designated intervention policy	0.006	[57]
φ	Percentage of detected HCV-infected individuals	0.3	[57, 72]
$\psi_{i,s}$	Annual rate of new drug injectors per age group i and gender s		Calibrated according to Florentin and Gorbatov (2009), United Nations Office on Drugs and Crime (2019)
c_H	Perceived financial costs due to mortality from HCV	$330,000	Israeli Ministry of Health
c_C	Perceived financial costs due to HCV-infected individual's checkup	$160	Israeli Ministry of Health
c_E	Fixed cost for a single HCV examination (screening)	$40	Israeli Ministry of Health
a	Elasticity coefficient representing the change in the willingness of individuals to be screened. Affects the country's total costs of screening function $C(s)$	$0 - 0.1$	
v	The financial value of one life year (QALY)	$40,000 - $120,000	Corresponds to 1–3 GDP per capita in Israel
r	Annual discount rate	0.03	

financial risk associated with the treatment and charges only if the treatment is successful. Finally, we consider a nonlinear pricing strategy in which the PC implements a volume-based discount pricing mechanism. In this case, the game begins with the PC announcing simultaneously the treatment cost p and a threshold z, where all treatments up to z are provided at the corresponding price p and all treatments beyond z are provided to the country free of charge. Afterward, the country determines simultaneously a treatment, checkup and a one-time screening policy at time $t = t_c$. This modification affects the treatment cost component in both players' utility functions, where the number of treatments that the country finances is the minimum between the actual number of treated individuals and the threshold defined by the PC.

4 Dataset and simulation results

We performed simulation studies parametrized based on data describing the epidemiology of HCV-infected patients in Israel to calculate the utility of the players for each strategy chosen. Israel is a good candidate for exploring the mechanism between a PC and a country. The country maintains a centralized policy, in which the Israeli Health Committee negotiates the price of treatment and covers the treatment for its citizens. Approximately 100,000

individuals (~ 1.25% of the population) are infected with HCV, and 70% are unaware of their infection [57]. It is estimated that 0.5% of the population aged 15–64 in Israel inject drugs, of which 67% are infected with HCV [69].

We conducted simulation studies using the full transmission models, including additional stratification of individuals based on gender and age group (Appendix 1). The IDU population was also stratified based on IDU status (Appendix 2), with an initial HR coverage of 40% [60, 70]. The model includes epidemiological, immunological, sociodemographic, as well as economic and operational parameters, which were estimated based on the relevant literature (Table 1). Missing epidemiological parameters were evaluated by calibrating the model to data from a previous study on HCV epidemiology in Israel in 2012 [57]. Note that the disease is asymptomatic until its fatal final stage. Therefore, we assumed no difference between a healthy individual and an infected individual in terms of the quality of life-years.

4.1 Model parameters

The population was stratified into 16 age groups: 0–4 years, 5–9 years, 10–14 years, 15–19 years, 20–24 years, 25–29 years, 30–34 years, 35–39 years, 40–44 years, 45–49 years, 50–54 years, 55–59 years, 60–64 years, 65–69 years, 70–74 years, and over 75 years of age. We

considered injection behavior may initiate from the age of 15, in accordance with [69, 73, 74]; thus, the IDU population consists of the last 13 groups. The annual natural mortality rates for each age group i and gender s were parametrized based on the Israeli Central Bureau of Statistics (ICBS). In addition, we also assessed these mortality rates according to each of the u IDU types—$\mu_{i,s}^{u}$ [59].

Disease progression rates $\beta_{f,i,s}$ for disease stage f, age group i, and gender s were extracted from large retrospective cohort studies [71]. The efficacy of treatment varied widely with the stage of infection and was determined based on previous clinical trials [17]. These estimates suggest that treating at fibrosis stage 0 is very likely to be effective, with 98% efficacy, while treatment efficacy drops to 79% at fibrosis stage 3. We assume injection drug use does not affect adherence and response to treatment; thus, we assume similar treatment efficacy between IDUs and non-IDUs [75, 76].

Most HCV-infected individuals in Israel are unaware of their infection. To determine the proportion of individuals with reported HCV, we used a previous study that randomly tested individuals for HCV in Maccabi Healthcare Services, a 2-million-member health maintenance organization in Israel [57]. Based on their estimates and another national report [72], approximately 30% of the population are aware of their infection. The spontaneous annual screening rate before a designated intervention policy, γ, was estimated based on a study that concluded that a total of 6,150 patients were identified with newly diagnosed HCV between 2003–2012, out of approximately 100,000 individuals infected with HCV, resulting in a rate of 0.006 [57]. These estimates are similar to trends observed in the US (Kershenobich et al. [77], which projected a decrease in the proportion of HCV that is undiagnosed from approximately 50% in 2009 to 80% in 2021).

Cost-effectiveness analysis (CEA) of medical intervention considers the balance between the incremental cost of the intervention and the incremental health benefits attributable to the intervention. In our model, the financial value of QALY, v, was based on the terminology suggested by the WHO [51]. Their criteria define "cost-effective" as lower than three times the annual per capita gross domestic product (GDP) and "very cost-effective" as lower than the GDP. Accordingly, in the simulations, we considered $v = \$40,000$ and $\$120,000$, corresponding to Israel's GDP per capita and three times its GDP per capita, respectively. All costs and effects were discounted by an annual factor of 3%, similar to previous CEA studies in Israel [78].

For screening costs, we considered the function $C(s) = \left(c_E \cdot (1-a) \cdot s \right)^{\frac{1}{1-a}}$, where c_E is the fixed cost for a single HCV examination (i.e., screening) and a is a parameter that reflects the change in the willingness of the population to be screened ($0 \leq a \leq 1$). This function satisfies the conditions presented in 3.1 and is based on the same rationale as the isoelastic function, which is used in the context of standard economics [79]. Note that if $a = 0$, $C(s) = c_E \cdot s$, leading to a linear cost of screening.

4.2 Model calibration

The only parameter calibrated in the model is the blood transfusion rate ϱ. Our calibration process is based on detailed data on HCV prevalence in Israel from 2012 stratified by age and gender. To estimate this missing parameter, we ran simulations of the full transmission model (detailed in Appendices 1 and 2) from 1950 (a few years after the establishment of the state of Israel) to 2012, with an initial condition of 1,100 patients, similar to the assumptions of a previous model [80]. We calibrated the blood transfusion infection rate ϱ that minimized the mean squared error (MSE), which is equivalent to the maximum likelihood estimator (MLE) assuming that the error is normally distributed with a mean of zero (Figs. 3A and B). The number of infected individuals in each fibrosis stage obtained by our calibrated model was also validated using partial data from the Polaris observatory website [81] and a previous study in Israel [82]. This analysis reveals that advanced fibrosis stage prevalence increases with age, in line with [81] (Appendix 4).

4.3 Simulation studies

We conducted simulations to evaluate the players' strategies and utilities at equilibrium for the basic model and the two extensions (all decision variables are detailed in Table 2). Due to transmission within the IDU population, elimination after mortality (related or unrelated to HCV) is not necessarily within reach. Thus, in typical health economics, the effectiveness of a possible policy is analyzed based on a fixed cohort in a finite horizon [83]. We consider the cohort as individuals that were part of the population during the course of 50 years. We calculated the utilities for the country and the PC (see Appendix 5) for all individuals in the cohort throughout their entire lifetime. Namely, no new births or new HCV cases were considered 50 years into the simulation, and henceforth we analytically calculate the utilities until the cohort elimination.

We calculated the country's gain by comparing each treatment policy at time $t = t_c$ to a baseline policy, in which no treatment is considered. Thus, we defined the country's gain as the difference between the country's utility and the baseline utility. Using grid search for each set of decision variables (Table 2), the optimal policy chosen by the country for each treatment cost and quantity discount threshold is the one that maximizes its gain. Then, using backward induction, given each set of the country's decision variables for a specific treatment price, we calculated the PC's utility function. For the basic model and all the extensions, we analyzed the PC's utility and country gain for each treatment price. The equilibrium point is the point that maximizes the

Fig. 3 Calibration results for the initial number of infected individuals in 2012, compared to the data in the literature (hatched bars), divided by gender – women (**A**) and men (**B**)
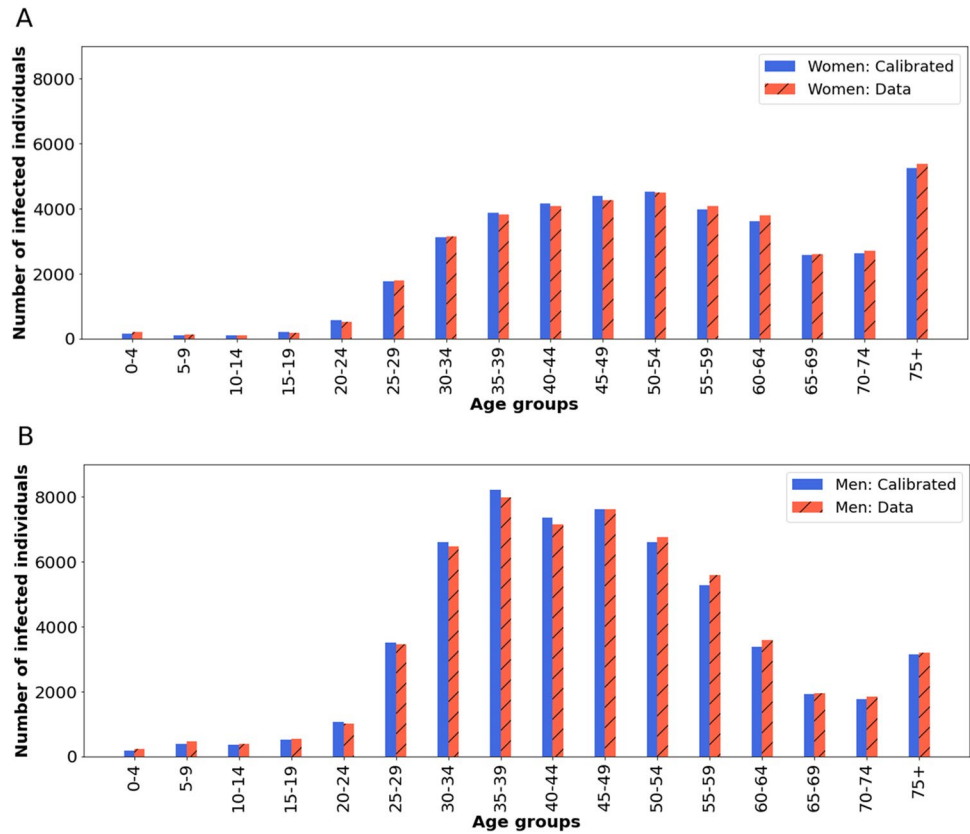
Table 2 Decision variables used in our model (The decision variables that are used in the extended models are presented without symbols)

Symbol	Parameter	Values considered
x	Country's policy for treatment. A tuple (f, a), where f is a binary vector depicting which fibrosis states are to be treated and a defines the oldest age group to be treated	$i \in f$, $a = \{0 - 4\,years, 5 - 9\,years, 10 - 14\,years, \ldots, 70 - 74\,years, 75 + \,years of age)$
y	Checkup rates per year for each diagnosed stage d	$y_d \in \left\{ \frac{1}{5}, \frac{1}{4}, \frac{1}{3}, \frac{1}{2}, 1, \frac{3}{2}, 2 \right\} \frac{checkups}{year}$
p	Treatment price set by the PC	$\$0 - \$200,000$
–	The year in which the screening campaign is conducted (when applicable)	$0 - 14\,years$
–	Number of individuals tested in the screening campaign (when applicable)	$0 - 7,500,000\,individuals$
–	Threshold value for quantity discount (when applicable)	$0 - 45,000\,treated individuals$

PC's utility, given the country's optimal decision. From a practical standpoint, if there is more than one equilibrium, we choose the equilibrium with the lowest treatment price.

4.4 Simulation results

4.4.1 Basic model

In these settings, the PC chooses the fixed treatment price per course. Afterward, the country determines its optimal policy for treatment in terms of fibrosis stage, age and checkup rate per diagnosed disease stage. Since the treatment coverage policy selects groups (by stage of disease and age group) that vary in size, the change in the utility of the PC is not linear (Fig. 4A).

We found that compared to no treatment, treatment is highly beneficial to PC and the country (Fig. 4). Assuming a willingness to pay of v=$40,000 per QALY gained, which corresponds to 1 GDP per capita, the price of treatment is expected to be $22,000 (Fig. 4A and B). The country's best response is to provide treatment to individuals above the age of 15 that are diagnosed with HCV at fibrosis stages

Fig. 4 Basic model's results – country treatment coverage policy and corresponding utilities for each treatment price. Comparison of utilities when the country's financial value equivalent to one healthy year is very cost-effective (green line) and cost-effective (dashed light-blue line) according to the WHO criteria, corresponding to 1 GDP per capita per QALY gained and 3GDP per capita per QALY gained, respectively. Stars mark the subgame perfect Nash equilibrium. (**A**) PC's utility. (**B**) Country's gain from treatment. (**C**) Discounted number of treated individuals. With the country's willingness to pay of 3GDP per capita instead of 1GDP per capita, the PC takes full advantage of the situation and doubles its revenue at equilibrium by increasing the price per treatment
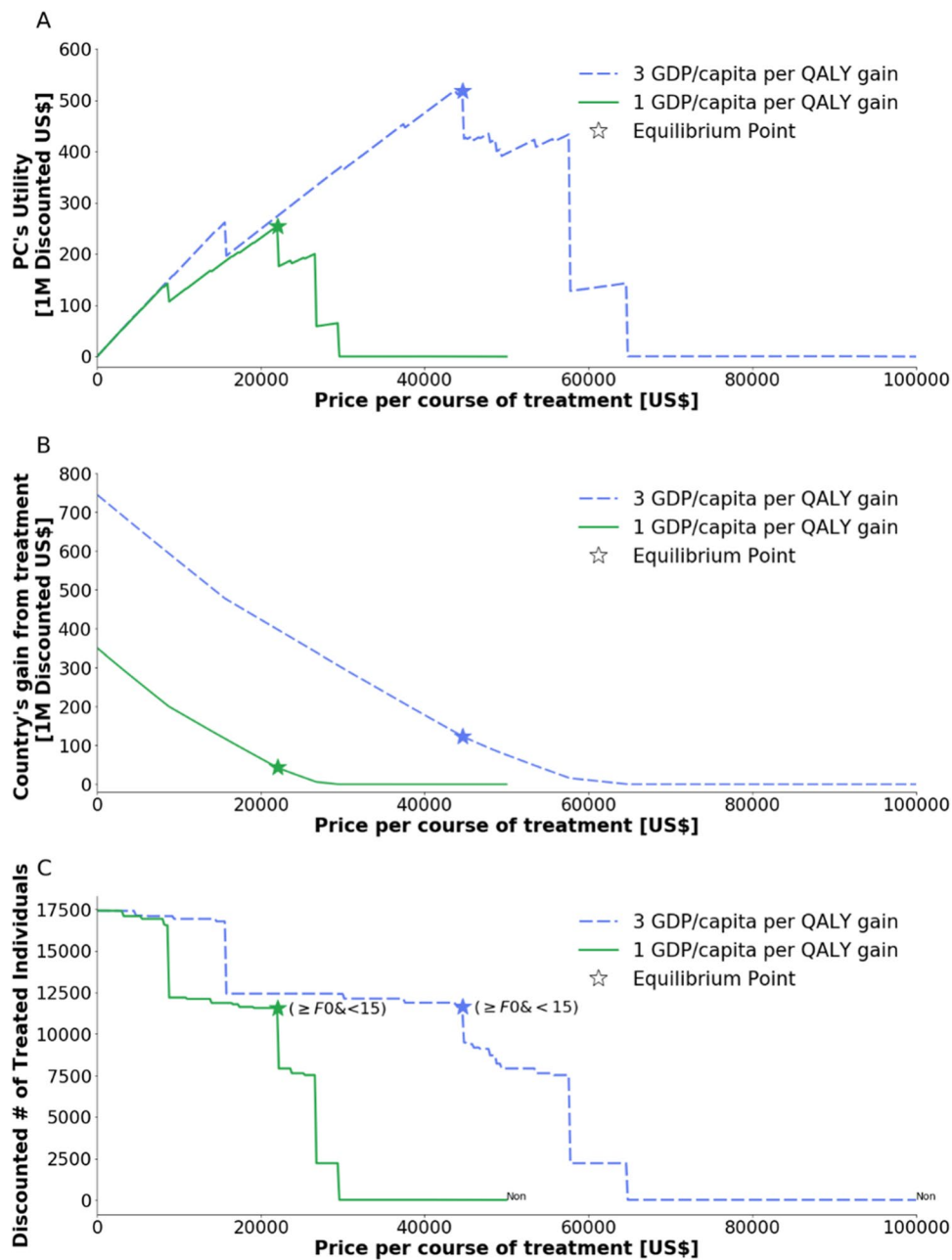

F1-F4, and individuals ages 15 and under diagnosed with HCV at stages F0-F4. Compared to a no-treatment policy, the country gains $43 million in average, whereas the average revenue of the PC is $254 million. If the willingness to pay per QALY gained increases, the PC is expected to considerably increase its revenue by charging more for the treatment. Consequently, most of the gain will transfer to the PC. For example, with a willingness to pay of $120,000 instead of $40,000 per QALY gain, the price per treatment will soar to $44,600. The utility of the PC will increase to $519 million, and the gain for the country compared to no treatment will be $123 million. Thus, 77% of the economic benefit (i.e., $519 M-$254 M vs. $123 M-$43 M)

will be transferred to the PC. Although the treatment policy remains the same, more checkups are conducted (biennial checkups for stage F2 instead of quadrennial. for both GDPs, quinquennial checkups are conducted for F0 and F1), resulting in a slight increase in the number of treated individuals.

4.4.2 Extension 1 – One-time screening funded by the country

In this extension, the PC chooses the fixed treatment price per course. Afterward, the country determines simultaneously the number of screened individuals in a one-time

Fig. 5 One-time screening results for different values of parameter a, which reflects the change in willingness for screening (Extension 1). Comparison of utilities with screening given $a = 0$ (dashed blue line) vs. screening given $a = 0.0015$ (dash-dotted dark-blue line) vs. no-screening policy (green line). Stars mark the subgame perfect Nash equilibrium. (**A**) PC's utility. (**B**) Country's gain from treatment. (**C**) Discounted number of treated individuals, with the financial value of one year parameter, v=$40,000. When the screening willingness parameter, a, is set to 0, the PC chooses a lower price per course of treatment than that chosen in the basic model. In return, the country chooses to screen the entire population, and both players gain from this scenario. For any treatment price higher than $11,200, the country does not perform any screening, regardless of the screening cost
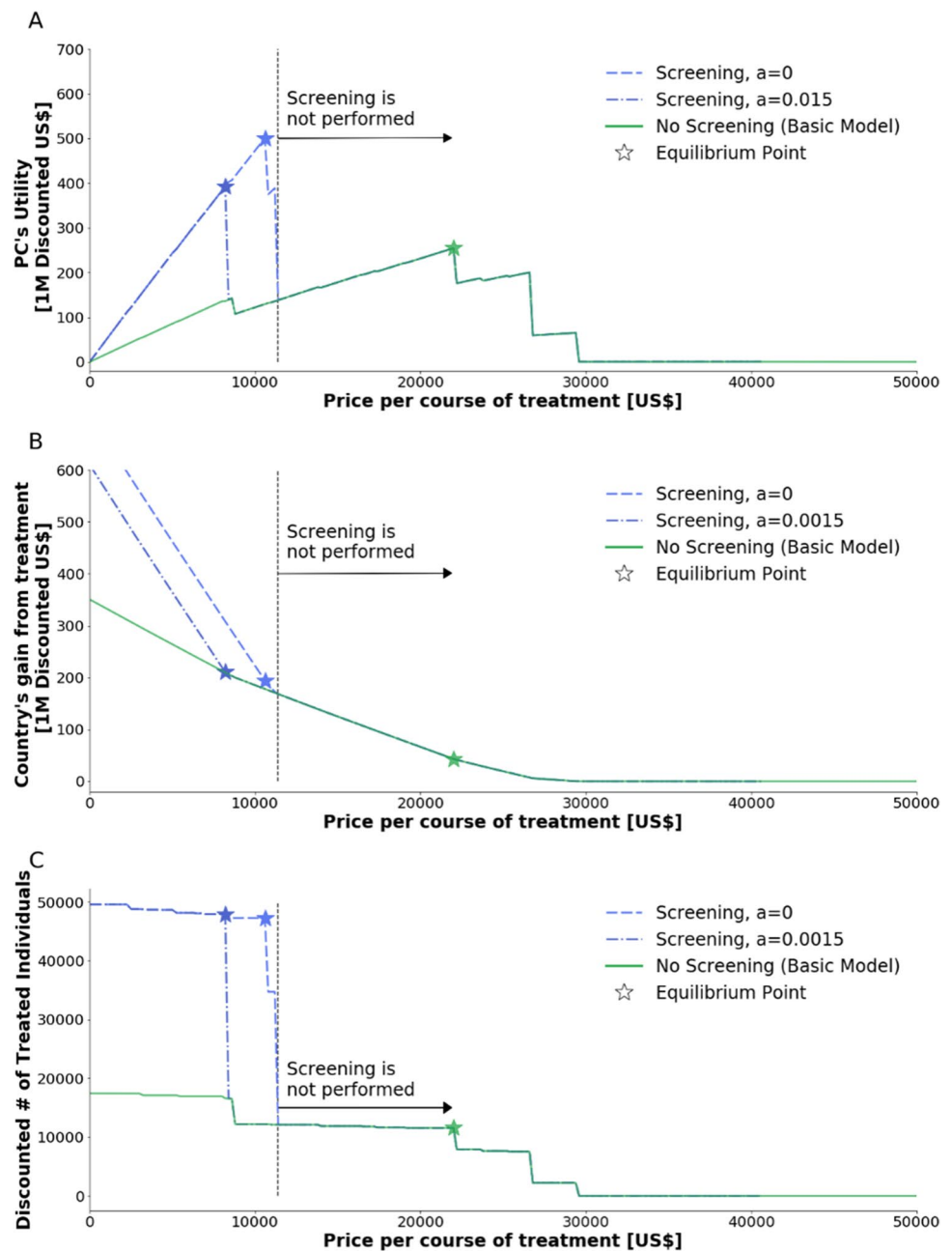
screening campaign as well as its treatment and check-up policies. We found that screenings that are covered by the country can further increase the utilities of both players. For example, if $v = \$40,000$, treatment is provided to all patients diagnosed from stage F1, similar to the basic model, but the optimal policy suggests also treating individuals under the age of 65 in stage F0 (compared to the age of 15 and below in the basic model). For low values of a, suggesting a relatively similar willingness of the population to be screened, both the PC and the country increase their utilities at equilibrium compared to the basic model (Fig. 5). The PC chooses

a treatment price per course of $10,600, less than half the price chosen in the basic model ($22,000). The country chooses to screen and treat all patients from fibrosis stage F0 and under the age of 65. By doing so, the PC and the country increase their discounted utilities by approximately $245 million and $151 million, respectively. For higher values of a, such that $a < 0.05$, the country decides to partially screen a portion of the population, while for $a \geq 0.05$, the country does not perform any screening, regardless of the treatment price. Our results suggest that for all values of a, the country chooses not to perform any screening for treatment prices

Fig. 6 Pricing mechanisms' effect on screening. Screening funded by the country (dashed blue line) vs. screening funded by the PC (dash-dotted brown line) vs. performance-based agreements (gray line). Stars mark the subgame perfect Nash equilibrium for each strategy. (**A**) PC's utility. (**B**) Country's gain from treatment. (**C**) Discounted number of treated individuals, all with the screening cost parameter a and the financial value of one year v set to set to 0 and $40,000, respectively. The PC increases its utility by funding screening, thereby forcing the country to conduct more screening than it would have desired, lowering the country's gain. Alternatively, performance-based agreements provide the country with additional flexibility to postpone treatment as treatment efficacy decreases with disease progression. They lead the PC to lower the price to increase the country's motivation for screening and early treatment
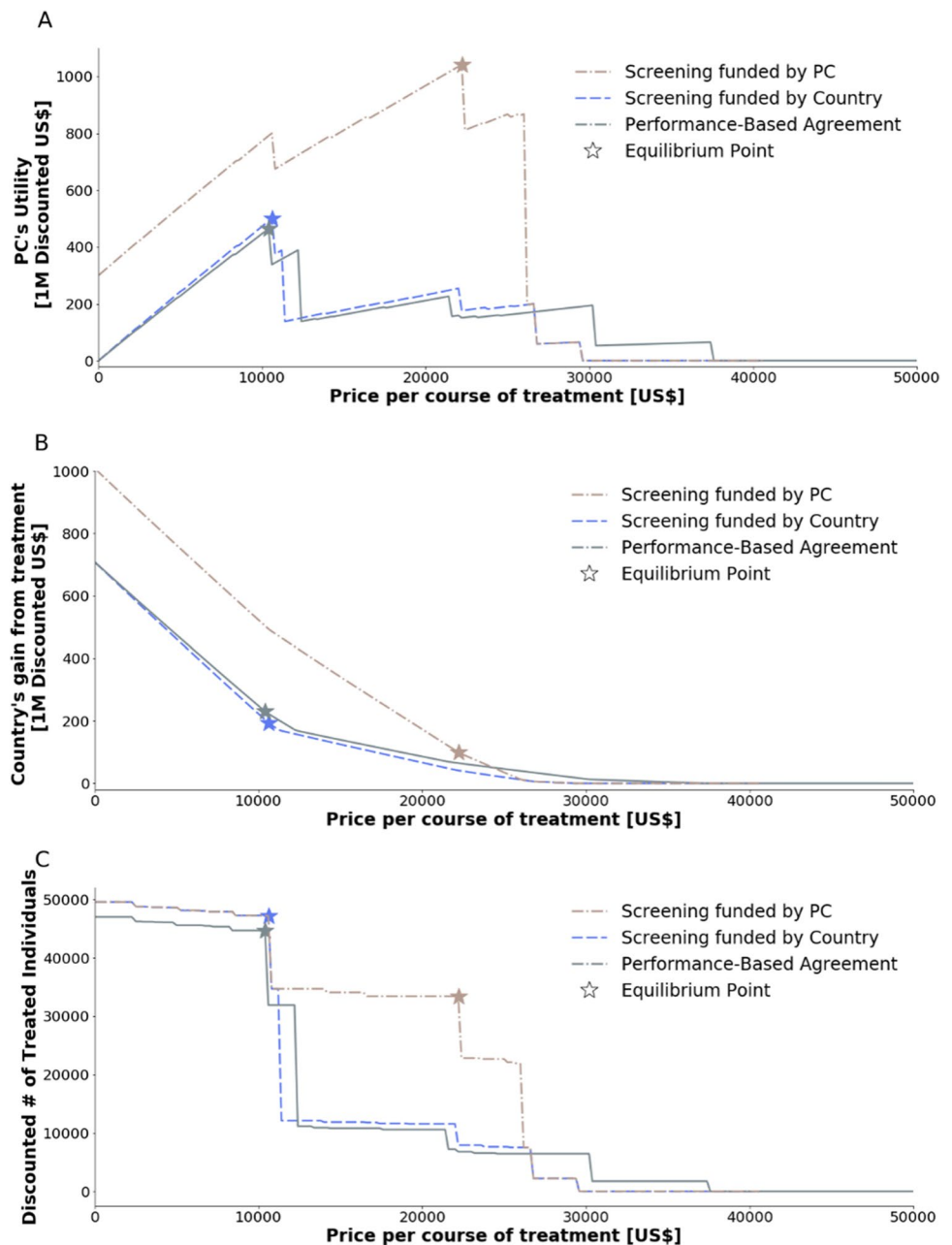
higher than $11,200. From this point, the model becomes identical to the basic model. The trends remain the same for all v values tested (Table 1). Thereby, results are henceforth shown for v=$40,000 per QALY gained, which corresponds to 1 GDP per capita.

4.4.3 Extension 2 – Pricing mechanisms

In this extension, we examine three pricing mechanisms observed in several developed countries:

One-time screening funded by the PC If the PC funds the screening, the PC achieves a superior outcome compared to a scenario in which the country funds the screening. This superior outcome is achieved because in equilibrium the treatment price rises to $22,200 (instead of $10,600), and as the number of treated individuals increases compared to a scenario where the country funds the screening. Counterintuitively, this case leads to a suboptimal outcome for the country as it forces the country to conduct more screening than it would have desired, lowering its gain compared to the latter. (Fig. 6).

Performance-based mechanism (Risk-sharing) In this case, the PC reimburses the country when treatment is unsuccessful. In other words, the country pays only for

Fig. 7 Quantity discount pricing results – Screening funded by the country (dashed blue line) vs. discount (dashed purple line) vs. fixed pricing per treatment (green line). Stars mark the subgame perfect Nash equilibrium for each strategy. (**A**) PC's utility. (**B**) Country's gain from treatment. (**C**) Discounted number of treated individuals, all with the screening cost parameter a and the financial value of one year v set to set to 0 and $40,000, respectively and v = $40,000. The PC increases its utility by applying a discount-for-quantity pricing mechanism. The utility of the country decreases even compared to that of the basic model
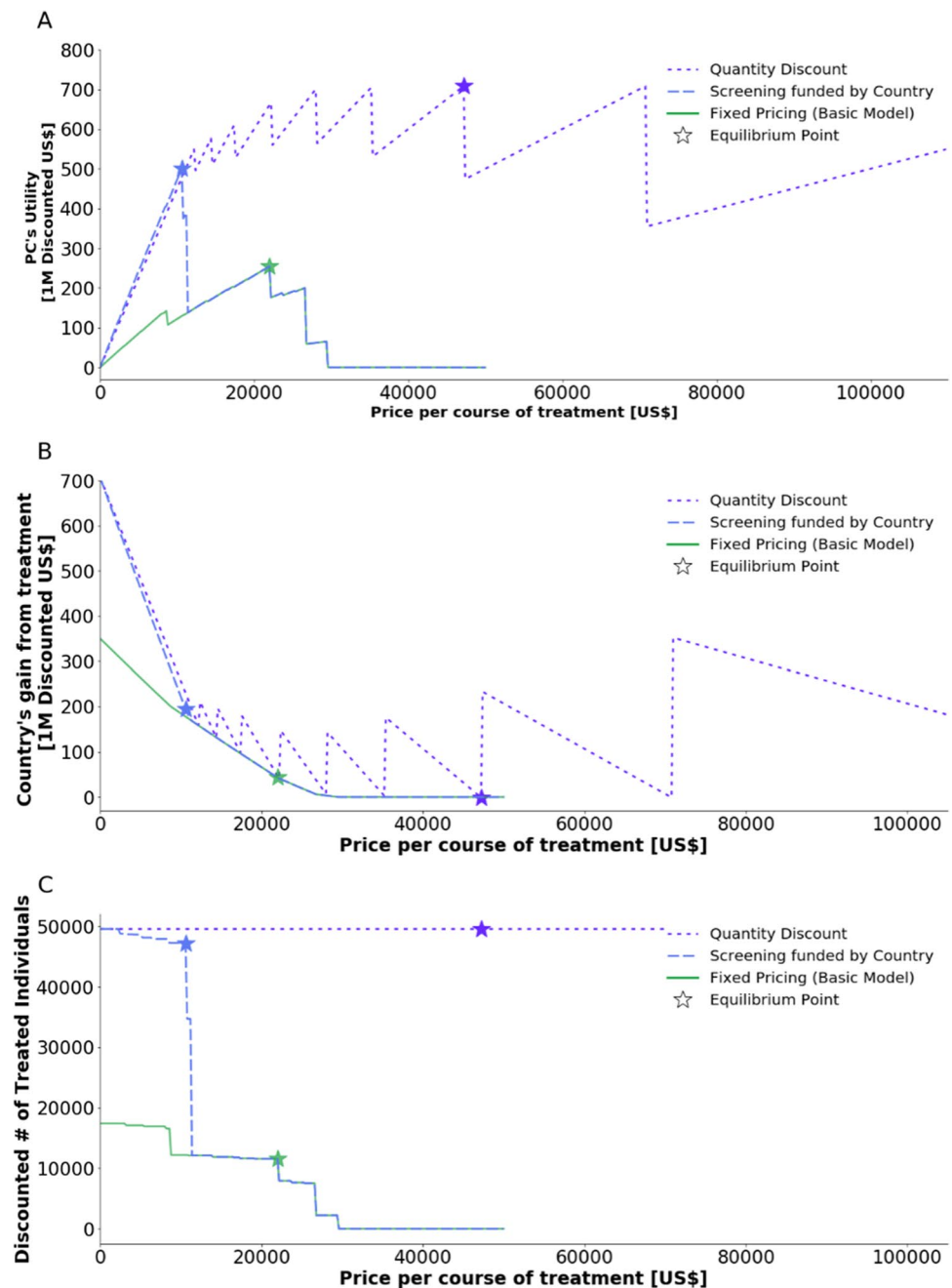

successful treatments. We found that this kind of mechanism is beneficial for the country. As treatment efficacy decreases with disease progression, performance-based agreements provide the country with additional flexibility to postpone treatment. In turn, it leads the PC to slightly lower the price ($10,400 instead of $10,600) to encourage the country to increase screenings and treat early (Fig. 6).

Quantity discount In this case, the PC chooses the fixed treatment price per course and applies a discount-for-quantity policy, allowing the country free treatment for all patients above a certain threshold. Afterward, the country decides its optimal policy for screening and treatment.

When the price of treatment is low, the PC chooses a very high threshold value to avoid loss. As the price of treatment increases, the PC lowers the threshold, incentivizing the country to increase the volume of treatments. The points at which the PC reduces its threshold value are the points at which the dashed purple line breaks (Fig. 7). At equilibrium, the PC sets a threshold of 15,000 individuals and a treatment price of $47,200. In contrast to the basic case and the first extension, where increasing the price of treatment causes the country to treat fewer patients, in this extension, the country's policy

Fig. 8 Annual probability of infection for an Active IDU vs. HCV prevalence among IDUs. The needle-sharing procedure reveals a strong concave effect for IDU transmission. The contribution of treating an IDU to decrease transmission is only marginal due to the nonlinearity of transmission through needle exchange
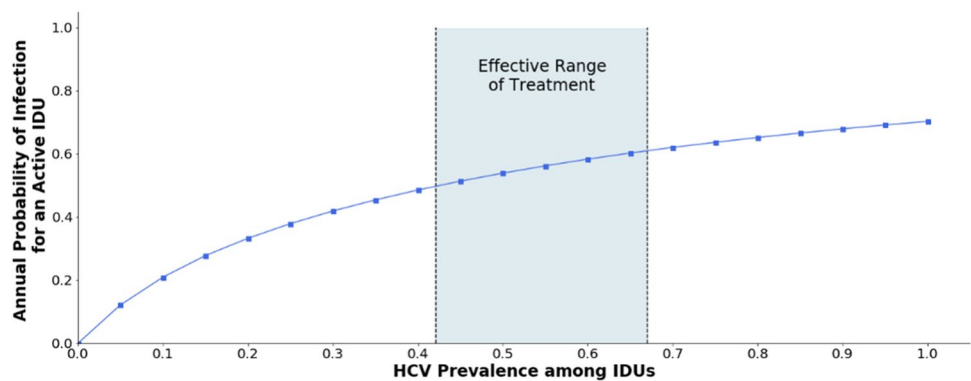
remains consistent: treat the entire diagnosed population. Since the country treats every diagnosed patient, no checkups are done. Our simulations show, for each of the values of a, the country's policy remains constant. Thus, increasing the treatment price affects only this parameter in the country's utility function; therefore, a symmetrical graph is obtained between the PC and the country's utility graphs (Fig. 7A and B).

The equilibrium point of the discount-for-quantity pricing mechanism achieves a suboptimal outcome for the country in terms of overall gain and a superior outcome for the PC in terms of utility compared to those achieved under a fixed pricing mechanism. This outcome is even less favorable than not conducting any screening at all (as shown in the basic model). Although there are treatment costs that can improve outcomes for both the PC and the country, they do not belong to the subgame perfect Nash equilibrium.

5 Discussion

We developed a game-theoretic model between a PC and a country to determine the optimal price of HCV treatment and the corresponding screening, checkup, and treatment strategies. Calibrated with detailed data from Israel, we found that with the standard fixed treatment pricing, applying a screening policy is beneficial to both the PC and the country. However, if the PC offers discounts for quantities or funding for screening, it will result in a suboptimal outcome for the country. Our simulations suggest that at equilibrium, a quantity discount or funding for screening force the country, either indirectly or directly, to conduct more screening and treat more individuals than it would have desired otherwise, lowering the country's gain.

By contrast, the country will gain from a mechanism in which the PC is required to cover the cost of unsuccessful treatments. One would expect that in such a mechanism, the PC would simply increase the price to balance their additional loss due to the inefficiency of the treatment. However, our

analysis indicated the opposite: as the efficacy of the treatment declines with disease progression, covering the price of unsuccessful treatment by the PC drives the country to postpone treatments. To avoid a potential postponement, the PC reduces the price of treatment in order to increase the country's motivation for screening and early treatment. Our work provides a rational explanation for the current agreements between countries and PCs [32–34, 84], including the PC's ethically questionable funding of screening programs [35, 36].

These key findings were strengthened when we extended the model to account for IDUs explicitly. The logic behind our findings is that, due to the strong concave effect of transmission through needle exchange (Appendix Fig. 8), the contribution of treating an IDU to decrease transmission is only marginal. Namely, to substantially reduce transmission due to needle exchange, a drastic behavioral change is required. These findings are in line with the results of several recent studies [85–87]. Moreover, IDUs who are treated and successfully clear the virus might return to needle-sharing behavior and are at a high risk of becoming reinfected with HCV. Finally, the life expectancy of IDUs is shorter than the non-IDUs: they are more likely to die from other causes unrelated to HCV due to their high-risk lifestyle. Thus, from an economic perspective, treating IDUs is less beneficial because fewer QALYs are saved. Consequently, the lower economic benefit reduces a country's willingness to pay for treatment, which further enhances the gap between the interests of the country and the PC.

Our simulations further indicated that even if the entire IDUs population is screened for HCV, and all eligible individuals (i.e., IDUs in HR or former IDUs) are treated, HCV will not be eliminated. Thus, we believe that treatment alone is not likely to reach the WHO targets and achieve viral elimination [18]. Multiple interventions, including treatment, scaled-up HR, and needle exchange programs that are jointly conducted, should be examined. The effectiveness and cost-effectiveness of such strategies can be more accurately evaluated using network-based models (See, for example, [88, 89]).

Our model has several potential limitations. First, the findings obtained from the simulations are based on data that are specific to Israel and thus might not apply to other countries. Specifically, disease prevalence varies widely in different regions of the world [90, 91], as does the proportion of HCV-infected individuals who are undiagnosed. In addition, there is considerable uncertainty regarding IDU risk behavior, in particular, the risk of becoming reinfected for those who joined an HR program. Nevertheless, given the wide range of parameter values considered, we expect that the observed trends are broadly the same for most developed countries. From a broader perspective, our model provides a general framework that can be applied to many other healthcare settings where screening is essential to determine treatment strategies.

Second, our model suggests favoring treatment for younger age groups. The economic justification for that observation is clear. Younger individuals have more years to lose and have a higher probability of reaching end-stage cirrhosis later in their lives. This result might raise an ethical question of age-based discrimination. While our model provides insights from a health economics perspective, public health policy makers may consider a wide range of factors when developing policies.

In addition, our model does not provide for screening focused sub-population groups other than IDUs. Clearly, the number of HCV patients among IDU is disproportionate, and thus, we tested screening policies that are based on IDU group. However, as results show, as treating IDUs is less beneficial for the country because fewer QALYs are saved, such focused screenings would only strengthen our key findings. Additional stratification for scanning is possible (e.g., based on ethnicity or age groups), but may raise additional ethical questions. Nevertheless, results show that the country achieves an inferior outcome even when it does not fund screening, and thus, although such policies would make the screening process more effective, we believe this will not change our main findings.

Our model does not consider future improvements in technologies that are likely to occur with time. A previous model highlighted that such improvements in technology can affect medical decision-making [92]. We expect that any improvement in technology would lower the checkup cost, providing the country with additional flexibility to postpone treatment, thereby intensifying our main results. In this context, it should be noted that the game model between the country and PC examined in this study does not include the management of negotiations between the parties nor any risk-sharing approaches examined in other studies [93, 94].

In conclusion, HCV is one of the leading causes of liver disease, causing massive public health and economic burden worldwide. In the US, it is estimated that 3.5 million people are chronically infected with HCV and that each year the disease is responsible for the deaths of 20,000 individuals – more than any other infectious disease before the COVID-19 pandemic [5]. Thus, the PC and the country appear to share a similar interest – treating as many HCV-infected individuals as possible. Moreover, as observed in several countries, allowing the PC to cover the cost of screening to identify more HCV-infected individuals or subsidizing treatment via discounts for quantities appears to benefit the public good. However, our work shows that the opposite is the case, namely, pharmaceutical companies, and not society at large, benefit, as they indirectly impose on the country to conduct more screening and treat more individuals than would be optimal for society. Counterintuitively, the results from our game model emphasize that allowing the PC to cover the cost of screening to identify infected patients might not be ethical and should be carefully evaluated by policy makers.

The logic behind our finding is that the clock is ticking differently for the PC and the country. HCV is a chronic illness that progresses slowly, and most HCV-infected individuals, in particular high-risk groups such as IDUs, will die naturally before reaching end-stage cirrhosis. Thus, given the inferior footing caused by discount-for-quantity treatment pricing, credible strategies that should be considered by the country include delaying screening and requiring the PC to cover the price of unsuccessful treatments. If such strategies are considered, the PC can be expected to respond by lowering the price to encourage the country to conduct screening as soon as possible. Eventually, a new equilibrium point that will mitigate the losses to society will be reached.

6 Appendix 1 – Transmission model – Non-IDU population

In the full transmission model, we generalize the set of difference equations that describe HCV disease progression, by the stage of the disease (f, d), age group $i \in \{0-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75+\}$ and gender $s \in \{female, male\}$. The stage of the disease is defined by two characteristics, f – the actual stage of fibrosis ($f \in \{0, 1, 2, 3, 4\}$) and d – the diagnosed stage, as observed in their most recent checkup test ($d \in \{-1, 0, 1, 2, 3, 4\}$). We assume that $f \geq d$, meaning an individual cannot be diagnosed in a more advanced stage than his actual stage.

For the general population, we account for two main transmission routes of HCV: 1) mother-to-infant transmission at birth and 2) contaminated blood dose via medical procedures. We denote $S_{i,s}(t)$, the number of non-IDU susceptible individuals per age group i and gender s. Entry into this state can result from new births either from an HCV-infected mother that did not transmit the disease or from a non-HCV mother. Another transition into this state can

result from growth from the previous age group, $i - 1$, at rate α_{i-1}. Transition out of this state can result from growth to the subsequent age group at rate α_i, disease infection via medical procedures ρ, drug addiction $\psi_{i,s}$ or natural death $\mu_{i,s}$. Hence, the change with time in the number of susceptible individuals, stratified by age group and gender is:

$$
\begin{aligned}
S_{i,s}&(t + \Delta t) - S_{i,s}(t) \\
&= \mathbb{1}_{i=1} \cdot \epsilon_s(t) \cdot \mathcal{N}_{i,s}(t) \cdot (1 - \kappa\omega(t)) + \alpha_{i-1} \cdot S_{i-1,s}(t) \\
&\quad - \left(\alpha_i + \rho \cdot \eta_{i,s}(t) + \psi_{i,s} + \mu_{i,s}\right)S_{i,s}(t),
\end{aligned} \tag{A1}
$$

where $\mathbb{1}_{i=1}$ is an indicator function taking a value one for the first age group, $i = 1$ and zero otherwise. For consistency $\alpha_0 = 0$, κ is the risk of infection during delivery and $\epsilon(t)$ is the birth rate at time t. Likewise, $\eta(t)$ is the proportion of HCV-infected individuals among the population who donate blood at time t, stratified by age and gender (see, for example, Vamvakas & Taswell (1994)), and $\omega(t)$ is the proportion of HCV-infected females among all fertile age groups i' in the population $\mathcal{N}_{i,s}(t)$:

$$
\omega(t) = \frac{\sum_{i' \in i} \sum_{s' \in s} \sum_{f' \in f} \sum_{d' \in d} I_{f',d',i',s'=female}}{\sum_{i' \in i} \mathcal{N}_{i',s=female}(t)} \tag{A2}
$$

$$
\eta(t) = \frac{\sum_{i' \in i} \sum_{s' \in s} \sum_{f' \in f} \sum_{d' \in d} v_{i,s} \cdot I_{f',d',i',s'}}{\sum_{i' \in i} \sum_{s' \in s} \sum_{f' \in f} \sum_{d' \in d} v_{i,s} \cdot \mathcal{N}_{f',d',i',s'}} \tag{A3}
$$

where $v_{i,s}$ is the rate of blood donation per age group i and gender s.

We assume that all newly infected individuals are not diagnosed and are at fibrosis stage F0; thus, entry to state $I_{0,-1}$ can occur due to infection $\lambda_{i,s}(t)$ or aging. Transition out of this state can result from growth to the subsequent age group at rate α_i, next stage of the disease $\beta_{f,i,s}$, the discovery of the disease γ, drug addiction $\psi_{i,s}$ or natural death $\mu_{i,s}$. As the patient has not been diagnosed at this state, no treatment is provided. The change with time in the number of undiagnosed infected individuals, stratified by age group and gender is:

$$
\begin{aligned}
I_{0,-1,i,s}&(t + \Delta t) - I_{0,-1,i,s}(t) \\
&= \mathbb{1}_{i=1} \cdot \epsilon_s(t) \cdot \mathcal{N}_{i,s}(t) \cdot \kappa\omega(t) + \lambda_{i,s}(t) \cdot S_{i,s}(t) + \alpha_{i-1}I_{0,-1,i-1,s}(t) \\
&\quad - (\alpha_i + \beta_{f,i,s} + \gamma + \psi_{i,s} + \mu_{i,s})I_{0,-1,i,s}(t)
\end{aligned} \tag{A4}
$$

where $\mathbb{1}_{i=1}$ is an indicator function taking a value one for the first age group, $i = 1$ and zero otherwise. We define $\mathcal{X}$ as a decision matrix describing the country's decision whether to treat an individual at presumed fibrosis stage d and age group i. Equation (A5) describes all the diagnosed states where $d = f$. Only when $\mathcal{X}_{f,i} = 0$, individuals at fibrosis stage f and age group i are not treated, and can enter these states at

rates y_i, $i \in \{-1, 0, 1, ..d - 1\}$ as a result of stage diagnosis (checkup). Similar to equation (A4), entry to these states derive from aging. Transition out of these states to others can result from growth to the next age group, next stage of the disease, drug addiction or natural death, respectively.

$$
\begin{aligned}
I_{f,d,i,s}&(t + \Delta t) - I_{f,d,i,s}(t) \\
&= \alpha_{i-1}I_{f,d,i-1,s}(t) + (1 - \mathcal{X}_{f,i})\sum_{j=-1}^{d-1} y_j I_{f,j,i,s}(t) \\
&\quad - (\alpha_i + \beta_{f,i,s} + \psi_{i,s} + \mu_{i,s})I_{f,d,i,s}(t), \; \forall d = f
\end{aligned} \tag{A5}
$$

Equation (A6) describes all other states (where $d < f$). For consistency, we marked $\beta_{4,i,s}$ as the mortality rate from HCV in group i and gender s and y_{-1} as the common HCV diagnosis rate γ [57].

$$
\begin{aligned}
I_{f,d,i,s}&(t + \Delta t) - I_{f,d,i,s}(t) \\
&= \alpha_{i-1}I_{f,d,i-1,s}(t) + \beta_{f-1,i,s}I_{f-1,d,i,s}(t) \\
&\quad - (\alpha_i + \beta_{f,i,s} + y_d + \psi_{i,s} + \mu_{i,s})I_{f,d,i,s}(t), \; \forall d < f
\end{aligned} \tag{A6}
$$

The treated population is divided into two groups: susceptible following treatment ($ST_{f,i,s}$) representing individuals for whom treatment was effective, and infected following treatment ($IT_{f,i,s}$), representing individuals for whom treatment was ineffective or individuals that were effectively treated but got re-infected. Let θ_f represent the efficacy of the treatment at stage f. An individual in stage f can be diagnosed at rates y_i, $i \in \{-1, 0, 1, ..., f-1\}$; then, when $\mathcal{X}_{f,i} = 1$ (the fibrosis stage and age group are treated by policy), the individual can transition to $ST_{f,i,s}$ if treatment is efficient with probability θ_f. Alternatively, the individual transitions to $IT_{f,i,s}$, if treatment is inefficient. Transition out of state $ST_{f,i,s}$ can result from growth to the subsequent age group at rate α_i, disease reinfection via medical procedures ρ, drug addiction $\psi_{i,s}$ or natural death $\mu_{i,s}$. Transition out of state $IT_{f,i,s}$ can result from growth to the subsequent age group at rate α_i, next stage of the disease $\beta_{f,i,s}$, drug addiction $\psi_{i,s}$ or natural death $\mu_{i,s}$. The changes with time in the number of treated individuals, stratified by age group and gender is:

$$
\begin{aligned}
ST_{f,i,s}&(t + \Delta t) - ST_{f,i,s}(t) \\
&= \alpha_{i-1}ST_{f,i-1,s} + \mathcal{X}_{f,i}\theta_f \sum_{j=-1}^{f-1} y_j I_{f,j,i,s} \\
&\quad - (\alpha_i + \rho + \psi_{i,s} + \mu_{i,s})ST_{f,i,s}
\end{aligned} \tag{A7}
$$

$$
\begin{aligned}
IT_{f,i,s}(t + \Delta t) - IT_{f,i,s}(t) &= \alpha_{i-1}IT_{f,i-1,s} + \mathcal{X}_{f,i}(1 - \theta_f)\sum_{j=-1}^{f-1} y_j I_{f,j,i,s} + \\
&\quad \beta_{f-1,i,s}IT_{f-1,i,s} + \rho \cdot ST_{f,i,s} - (\alpha_i + \beta_{f,i,s} + \psi_{i,s} + \mu_{i,s})IT_{f,i,s}.
\end{aligned} \tag{A8}
$$

The initial conditions are given by $l_{f,d,i,s}$, the initial number of infected individuals in each state, leading to equation (A9):

Table 3 Parameters used in the simulation for the initial number of infected individuals

Symbol	Parameter	Values Considered	Data Source
κ	Risk of infection during delivery	0.05	[95]
Fertile	Fertility age groups	$15 - 49$	Israeli Central Bureau of Statistics
$\epsilon_s(t)$	Birth rate of gender s at time t		Israeli Central Bureau of Statistics
D	Eligible blood donors' age groups	$20 - 59$	
ϱ	Blood transfusion infection rate	3.73	Estimated
$v_{i,s}(t)$	Rate of blood donation per age group i and gender s		[96], Israeli Central Bureau of Statistics
σ_s	The proportion of infected individuals that are not spontaneously cleared from HCV, defined by gender, s	55.4%—Female 66.3%—Male	[6]

$$
\begin{aligned}
I_{f,d,i,s}\left(t = t_c^-\right) &= l_{f,d,i,s} \\
S_{i,s}\left(t = t_c^-\right) &= \mathcal{N}_{i,s}(t) - \sum_{i \in f, f \geq d} \sum_{j \in d} I_{i,j}(t) \\
ST_{f,i,s}\left(t = t_c^-\right) &= 0 \\
IT_{f,i,s}\left(t = t_c^-\right) &= 0
\end{aligned}
\tag{A9}
$$

The rate at which individuals in age group i are infected with HCV at time t, that is the force of infection, is given by:

$$
\lambda_{i,s}(t) = \varrho \cdot \eta_{i,s}(t) \cdot \sigma_s,
\tag{A10}
$$

where σ_s is the proportion of infected individuals in gender s that had not been spontaneously cleared from the disease.

Table 3

7 Appendix 2 – Transmission model – Injecting drug users

In the IDU transmission model, we generalize the set of difference equations that describe HCV disease progression, by the stage of the disease (f, d), age group $i \in \{15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75+\}$, gender $s \in \{female, male\}$ and the IDU status $u \in \{ActiveIDU, IDUinHR, FormerIDU\}$.

The IDU transmission model accounts for an additional transmission route compared to the non-IDU transmission model, which is the sharing of contaminated injecting equipment. newly IDUs enter the active IDU group at rate ψ, where they can be either susceptible to HCV S^{Active}, infected with HCV I^{Active}, susceptible following treatment ST^{Active}, or infected following treatment IT^{Active}. For those already infected with HCV, the disease progresses as described in 2.2.2; thus, the I^{Active} subgroup includes 15 transient states that explicitly track the actual fibrosis stage (denoted by f) and presumed stage (denoted by d), i.e., $I_{f,d}^{Active}$. Similarly to the general model, as treatment will not be offered again after reinfection, the ST^{Active} and IT^{Active} subgroups include five states each to explicitly track the five possible stages of fibrosis, i.e., IT_f^{Active} and ST_f^{Active}. As previously suggested [59, 64],

and due to the considerable risk of reinfection [65], treatment is not offered to active IDUs. Nonetheless, individuals in the active IDU group may have already received treatment while in the IDU in HR group or the former-IDU group.

Newly-active IDUs enter the active IDU group from the Non-IDU population at rate $\psi_{i,s}$. IDUs who cease with drug-injection behavior remain in the IDU transmission model and are classified as former-IDUs. Other entries to the susceptible states result from growth from the previous age group, $i - 1$ at rate α_{i-1} or from a change in injection behavior at rate ζ. Transition out of these states can result from growth to the subsequent age group at rate α_i, disease infection $\lambda_{i,s}^u$, change in injection behavior ζ, or natural death $\mu_{i,s}^u$:

$$
\begin{aligned}
&S_{i,s}^u(t + \Delta t) - S_{i,s}^u(t) \\
&= \mathbb{1}_{u=IDU} \cdot S_{i,s}^{Non-IDU}(t) \cdot \psi_{i,s} + \alpha_{i-1} \cdot S_{i-1,s}^u(t) + \sum_{k \neq u} \zeta_{ku} \cdot S_{i,s}^k(t) \\
&\quad - \left(\alpha_i + \lambda_{i,s}^u(t) + \mu_{i,s}^u + \sum_{k \neq u} \zeta_{uk} \right) \cdot S_{i,s}^u(t),
\end{aligned}
\tag{B1}
$$

where $\mathbb{1}_{u=IDU}$ is an indicator function taking a value one for all $u = IDU$ and zero otherwise. Recall that $\alpha_0 = 0$. We assume that all newly infected individuals are not diagnosed and are at fibrosis stage F0; thus, entry to the state $I_{0,-1,i,s}^u$ can occur due to infection at rate $\lambda_{i,s}^u$, as a result of contaminated blood either via medical procedures or via shared injections (Appendix 3). Other entries to the infected subgroups derive from initiation of drug-use at rate ψ, aging at rate α_{i-1} and change in injection behavior ζ. Transition out of the infected subgroups to others at rates α_i, $\beta_{f,i,s}$, γ, ζ and $\mu_{i,s}^u$, can result from growth to the next age group, next stage of the disease, the discovery of the disease, change in injection behavior, or natural death, respectively.

$$
\begin{aligned}
&I_{0,-1,i,s}^u(t + \Delta t) - I_{0,-1,i,s}^u(t) \\
&= \mathbb{1}_{u=IDU} \cdot I_{0,-1,i,s}^{Non-IDU}(t) \cdot \psi_{i,s} + \alpha_{i-1} \cdot I_{0,-1,i-1,s}^u(t) + \lambda_{i,s}^u(t) \cdot S_{i,s}^u(t) \\
&\quad + \sum_{k \neq u} \zeta_{ku} \cdot I_{0,-1,i,s}^k(t) - \left(\alpha_i + \beta_{0,i,s} + \gamma + \mu_{i,s}^u + \sum_{k \neq u} \zeta_{uk} \right) \cdot I_{0,-1,i,s}^u(t)
\end{aligned}
\tag{B2}
$$

We define $\mathcal{X}$ as a decision matrix describing the country's decision whether to treat an individual at presumed

fibrosis stage d and age group i. Equation (B3) describes all the diagnosed states where $d = f$. Only when $\mathcal{X}_{f,i} = 0$, individuals at fibrosis stage f and age group i are not treated, and can enter these states at rates y_i, $i \in \{-1, 0, 1, ..d-1\}$ as a result of stage diagnosis (checkup). Similar to equation (B2), other entries to the infected subgroups derive from initiation of drug use, aging and transitions between IDU groups. Transition out of these states to others can result from progression to the next age group, next stage of the disease, change in injection behavior, or natural death, respectively.

$$
\begin{aligned}
&I^u_{f,d,i,s}(t + \Delta t) - I^u_{f,d,i,s}(t) \\
&= \mathbb{1}_{u=IDU} \cdot I^{Non-IDU}_{f,d,i,s}(t) \cdot \psi_{i,s} + \alpha_{i-1} \cdot I^u_{f,d,i-1,s} \\
&+ (1 - \mathcal{X}_{f,i}) \sum_{j=-1}^{d-1} y_j \cdot I^u_{f,j,i,s}(t) + \sum_{k \neq u} \zeta_{ku} \cdot I^k_{f,d,i,s}(t) \\
&- \left(\alpha_i + \beta_{f,i,s} + \mu^u_{i,s} + \sum_{k \neq u} \zeta_{uk} \right) \cdot I^u_{f,d,i,s}(t), \forall d = f
\end{aligned}
\tag{B3}
$$

Equation (B4) describes all other states (where $d < f$). Transition into these states occur at rates ψ, α_{i-1} and $\beta_{f-1,i,s}$ from initiation of drug use, aging, or from disease progression, respectively. Transition out of these states occur at rates $\alpha_i, \beta_{f,i,s}, y_d, \zeta$ and $\mu_{i,s}$ can result from growth to the next age group, next stage of the disease, stage diagnosis (checkup), change in injection behavior, or non-HCV death, respectively. For consistency, we marked $\beta_{4,i,s}$ as the mortality rate from HCV in group i and gender s and y_{-1} as the common HCV diagnosis rate γ [57].

$$
\begin{aligned}
&I^u_{f,d,i,s}(t + \Delta t) - I^u_{f,d,i,s}(t) \\
&= \mathbb{1}_{u=IDU} \cdot I^{Non-IDU}_{f,d,i,s}(t) \cdot \psi_{i,s} + \alpha_{i-1} \cdot I^u_{f,d,i-1,s} + \beta_{f-1,i,s} \cdot I^u_{f-1,d,i,s} \\
&+ \sum_{k \neq u} \zeta_{ku} \cdot I^k_{f,d,i,s}(t) - \left(\alpha_i + \beta_{f,i,s} + y_d + \mu^u_{i,s} + \sum_{k \neq u} \zeta_{uk} \right) \cdot I^u_{f,d,i,s}(t), \forall d < f
\end{aligned}
\tag{B4}
$$

The IDU treated population at fibrosis stage f, age group i and gender s is divided into two groups: susceptible following treatment (ST) representing individuals for whom treatment was effective, and infected following treatment (IT), representing individuals for whom treatment was not effective or individuals that were effectively treated but got re-infected. Individuals can either transition into the IDU treated population from the Non-IDU treated population at rate ψ or following treatment from the IDU population. Let θ_f represent the efficacy of the treatment at stage f. An individual in stage f can be diagnosed at rates y_i, $i \in \{0, 1, ..., f-1\}$; then, when $\mathcal{X}_{f,i} = 1$ (the fibrosis stage and age group are treated by policy), the individual can transition into $ST^u_{f,i,s}$ with probability θ_f, meaning, the treatment was efficient. Alternatively, the individual transitions to $IT^u_{f,i,s}$, if treatment was inefficient. Recall that although the virus is cleared, the liver condition remains unchanged due to the very slow regression of fibrosis [58]; thus,

individuals transition with an identical fibrosis stage (e.g., $I^{HR}_{f=3,d=2} \rightarrow ST^{HR}_{f=3}$). Transitioning from state $ST^u_{f,i,s}$ can occur at rates α_i, $\lambda^u_{i,s}$, ζ and $\mu_{i,s}$ resulting from aging, disease transmission, change in injection behavior, or non-HCV death, respectively. Transitioning from state $IT^u_{f,i,s}$ can occur at rates α_i, $\beta_{f,i,s}$, ζ and $\mu_{i,s}$ resulting from growth to the next age group, to the next stage of the disease, change in injection behavior and a non-HCV death, respectively. The change with time in the number of treated individuals, stratified by age group and gender is:

$$
\begin{aligned}
&ST^u_{f,i,s}(t + \Delta t) - ST^u_{f,i,s}(t) \\
&= \mathbb{1}_{u=IDU} \cdot ST^{Non-IDU}_{f,i,s}(t) \cdot \psi_{i,s} + \alpha_{i-1} \cdot ST^u_{f,i-1,s} + \mathcal{X}_{f,i} \cdot \theta_f \\
&\cdot \sum_{j=-1}^{d-1} y_j \cdot I^u_{f,j,i,s}(t) + \sum_{k \neq u} \zeta_{ku} \cdot ST^k_{f,i,s}(t) - \left(\alpha_i + \lambda^u_{i,s}(t) + \mu^u_{i,s} + \sum_{k \neq u} \zeta_{uk} \right) \cdot ST^u_{f,i,s}(t)
\end{aligned}
\tag{B5}
$$

$$
\begin{aligned}
&IT^u_{f,i,s}(t + \Delta t) - IT^u_{f,i,s}(t) \\
&= \mathbb{1}_{u=IDU} \cdot IT^{Non-IDU}_{f,i,s}(t) \cdot \psi_{i,s} + \alpha_{i-1} \cdot IT^u_{f,i-1,s} + \mathcal{X}_{f,i} \cdot (1 - \theta_f) \\
&\cdot \sum_{j=-1}^{d-1} y_j \cdot I^u_{f,j,i,s}(t) + \beta_{f-1,i,s} \cdot IT^u_{f-1,i,s} + \lambda^u_{i,s}(t) \cdot ST^u_{f,i,s} + \sum_{k \neq u} \zeta_{ku} \cdot IT^k_{f,i,s}(t) \\
&- \left(\alpha_i + \beta_{f,i,s} + \mu^u_{i,s} + \sum_{k \neq u} \zeta_{uk} \right) \cdot IT^u_{f,i,s}(t)
\end{aligned}
\tag{B6}
$$

The initial conditions are given by $l^u_{f,d,i,s}$, the initial number of infected IDUs in each state, leading to equation (B7):

$$
\begin{aligned}
I^u_{f,d,i,s}\left(t = t_c^-\right) &= l^u_{f,d,i,s} \\
S^u_{i,s}\left(t = t_c^-\right) &= \mathcal{N}^u_{i,s}(t) - \sum_{i \in f, f \geq d} \sum_{j \in d} I_{i,j}(t) \\
ST^u_{f,i,s}\left(t = t_c^-\right) &= 0 \\
IT^u_{f,i,s}\left(t = t_c^-\right) &= 0
\end{aligned}
\tag{B7}
$$

8 Appendix 3 – Transmission due to needle exchange

The rate at which individuals transition to the infected groups I^{Active}, I^{HR}, IT^{Active}, and IT^{HR} arises from the sharing of contaminated injecting equipment. Inspired by Kaplan's notion of needle circulation from the moment of introduction into a population of IDUs [66, 67], we developed a nonlinear framework to model the force of infection due to needle exchange. First, we compute the proportion of contaminated needle sharing at time $C(t)$,

$$
C(t) = \frac{\varsigma_{Active} \left| I^{Active}(t) + IT^{Active}(t) \right| + \varsigma_{HR} \left| I^{HR}(t) + IT^{HR}(t) \right|}{\varsigma_{Active} \left| N^{Active}(t) \right| + \varsigma_{HR} \left| N^{HR}(t) \right|},
\tag{C1}
$$

where $|M|$ is the number of individuals in group M and ς_{Active} and ς_{HR} are the rates of needle sharing among active IDUs and among IDUs in HR, respectively. Let Z be a random variable describing an individual's order of using a needle.

Assuming homogenous mixing, the probability of becoming infected given injecting with a needle ordered Z is:

$$1 - (1 - g \cdot C(t))^{z-1}, \tag{C2}$$

where g is the probability of becoming infected given exposure to a contaminated needle. Let W be a random variable representing the number of times a needle is used (see, for example, Hopkins [98] and Judd et al. [99]). Note that $Pr_Z(z;t|w) = \frac{1}{w}$; thus, the rate of becoming infected by using a contaminated needle $p(t)$ is:

$$\xi_s(t) = m \cdot \sigma_s \cdot \sum_w Pr_W(w) \cdot \sum_{z=1}^{w} \frac{1}{w} \left(1 - (1 - g \cdot C(t))^{z-1}\right), \tag{C3}$$

where m is the rate of shared injections, and σ_s is the probability that the individual will not spontaneously clear the

virus. The force of infection $\lambda_{i,s}^{u}(t)$ in IDU group u consists of the rate of becoming infected through contaminated blood either by via a contaminated needle or via medical procedures:

$$\lambda_{i,s}^{u}(t) = \mathbb{1}_{u \in \{IDU, HR\}} \cdot \xi_s(t) + \rho \cdot \eta_{i,s}(t) \cdot \sigma_s, \tag{C4}$$

where $\mathbb{1}_{u \in \{IDU, HR\}}$ is an indicator function taking a value one for all $u \in \{IDU, HR\}$ and zero otherwise.

Figure 8

9 Appendix 4 – Simulation analysis to estimate initial number of infected individuals

Figure 9

Fig. 9 Initial number of infected individuals in 2012, derived from our calibration process, by IDU group in (**A**) and by stages of the disease (**B**). Advanced fibrosis stage prevalence increases with age
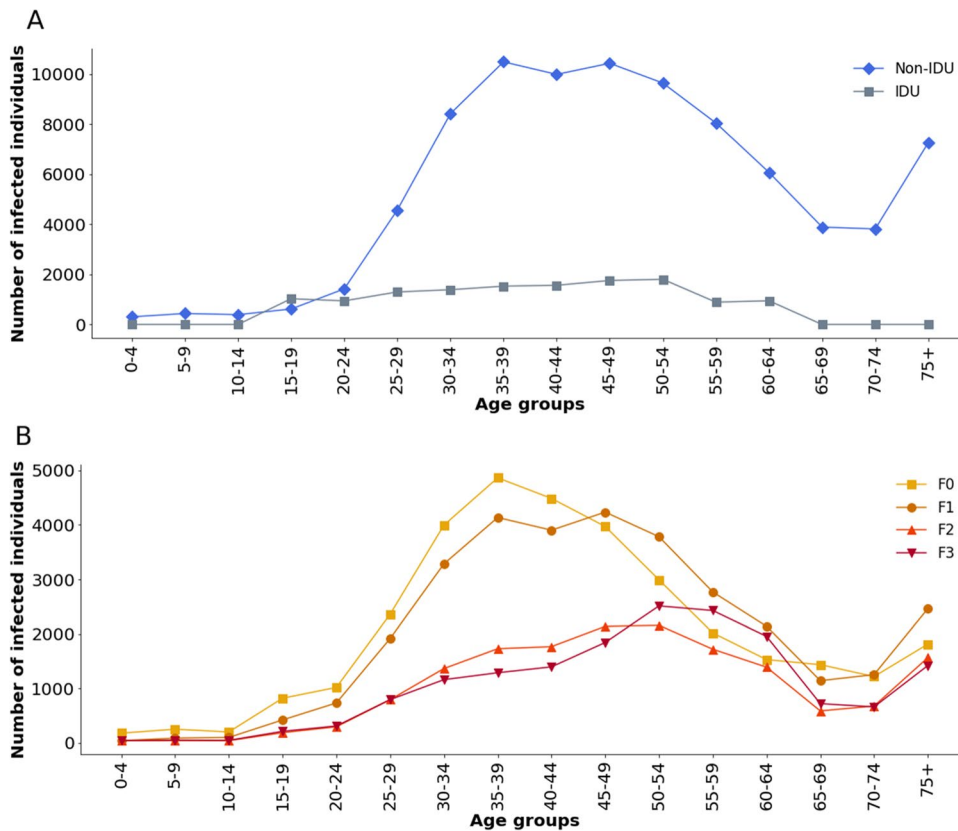
10 Appendix 5 – Detailed calculation of utility functions

We calculate the PC utility using absorbing Markov Chain's expected-time-to-absorption formula [97]. Let an absorbing Markov chain with k states, out of which q are transient and $k - q$ are absorbing states. The transition matrix $\widetilde{P}$ can be written as:

$$\widetilde{P} = \begin{pmatrix} \widetilde{Q}(x,y) & \widetilde{R} \\ 0 & \widetilde{I}_r \end{pmatrix}, \tag{E1}$$

where $\widetilde{Q}(x,y)$ is a qxq matrix, describing the probability of transitioning from some transient state to another in one step, $\widetilde{R}$ describes the probability of transitioning from some transient state to some absorbing state, and $\widetilde{I}_r$ is a $(k-q)x(k-q)$ identity matrix. '~' represents the omission of financial discounting, which is presented next. Multiplying each transition rate by Δt, such that $\Delta t \to 0$, and scaling each step of the difference equations to 1 unit defines a probability matrix, in line with the differential equations we described in Sect. 2.2.2, as:

$$\widetilde{Q}(x,y) = \begin{array}{c} I_{0,-1} \\ I_{1,-1} \\ \vdots \\ ST_0 \\ \vdots \end{array} \begin{pmatrix} 1 - (\beta_0 + y_{-1} + \mu) & \beta_0 & 0 & \cdots \\ 0 & 1 - (\beta_1 + y_{-1} + \mu) & \beta_1 & \cdots \\ \vdots & \vdots & \vdots & \cdots \\ 0 & 0 & 0 & \cdots \\ \vdots & \vdots & \vdots & \ddots \end{pmatrix} \tag{E2}$$

According to [97], the expected time spent in each non-absorbing state, $\widetilde{H}(x,y)$, is given by:

$$\widetilde{H}(x,y) = \left(I - \widetilde{Q}(x,y) \right)^{-1}. \tag{E3}$$

In addition, the probability of being absorbed in each absorbing state from any transient state, $\widetilde{A}(x,y)$, is given by:

$$\widetilde{A}(x,y) = \widetilde{H}(x,y) \cdot \widetilde{R}. \tag{E4}$$

To explicitly track treated individuals at their actual time of treatment, we aggregate all the treatment states (ST_f and IT_f) into two absorbing states, resulting in an additional Markov chain consisting of 4 absorbing states: two representing death ($m = 1, 2$) and two representing treatment. Solving similarly, the expected number of individuals treated against HCV from time $t > t_c$, $\widetilde{N}_{T_2}(x,y)$, is the dot product of a transposed vector representing the initial number of individuals in each pre-treatment transient state after treatment policy x is initially applied, $I^T\left(x, t = t_c + \Delta t\right)$, and the jth column of the $\widetilde{B}$ matrix, which is the equivalent of matrix $\widetilde{A}(x,y)$ in the other Markov process. This matrix represents the probabilities to transition from each pre-treatment transient state to the absorbing states representing treatment:

$$\widetilde{N}_{T_2}(x,y) = I^T\left(x, t = t_c + \Delta t\right) \cdot \left(\widetilde{B}(x,y)_{*,ST} + \widetilde{B}(x,y)_{*,IT} \right). \tag{E5}$$

Thus, the total number of individuals treated against HCV over an infinite horizon is composed of both the individuals that meet the treatment criteria when the treatment policy starts at time $= t_c$ $\left(\widetilde{N}_{T_1}(x,y) \right)$, and those discovered from time $t > t_c$ $\left(\widetilde{N}_{T_2}(x,y) \right)$:

$$\widetilde{N}_T(x,y) = \widetilde{N}_{T_1}(x,y) + \widetilde{N}_{T_2}(x,y) = \\ = \sum_{i=0, i \geq j}^{3} \sum_{j=-1}^{3} x_j I_{i,j}\left(t = t_c\right) + I^T\left(x, t = t_c + \Delta t\right) \cdot \left(\widetilde{B}(x,y)_{*,ST} + \widetilde{B}(x,y)_{*,IT} \right). \tag{E6}$$

In order to take into account financial discounting, we add to the transition matrix a dummy absorbing state, named "Capitalization". Dividing each transition rate by the discount value, $1 + r$, so that in each time step we only transfer the discounted individuals, and the remainder is transferred to the "Capitalization" state at a rate of $\left(1 - \frac{1}{1+r} \right)$. The P and Q matrices will be set accordingly to:

$$P = \begin{pmatrix} Q(x,y) & R \\ 0 & I_r \end{pmatrix}, \tag{E7}$$

$$Q(x,y) = \begin{pmatrix} \frac{1-(\beta_0+y_{-1}+\mu)}{1+r} & \frac{\beta_0}{1+r} & 0 & \frac{(1-x_0)y_{-1}}{1+r} & \cdots \\ 0 & \frac{1-(\beta_1+y_{-1}+\mu)}{1+r} & \frac{\beta_1}{1+r} & 0 & \cdots \\ \vdots & \vdots & \vdots & \vdots & \ddots \end{pmatrix} \tag{E8}$$

and the adjusted expected time spent in each non-absorbing state, $H(x,y)$, is given by:

$$H(x,y) = (I - Q(x,y))^{-1}. \tag{E9}$$

In addition, the discounted probability of being absorbed in each absorbing state from any transient state, $A(x,y)$, is given by:

$$A(x,y) = H(x,y) \cdot R. \tag{E10}$$

Consequently, we can calculate the total discounted number of individuals treated against HCV over an infinite horizon:

$$N_T(x,y) = \left(\sum_{i=0, i \geq j}^{3} \sum_{j=-1}^{3} x_j I_{i,j}\left(t = t_c\right) + I^T\left(x, t = t_c + \Delta t\right) \cdot \left(B(x,y)_{*,ST} + B(x,y)_{*,IT} \right) \right). \tag{E11}$$

As the country's utility also relies on the following discounted parameters over an infinite horizon, given policy: 1) $N_H(x,y)$ – expected number of individuals hospitalized due to HCV infections, 2) $N_C(x,y)$ – the total expected number of times that all individuals were checked to determine their

fibrosis stage and 3) $QALY(x, y)$ – the entire population's life expectancy in years, we can calculate accordingly:

$$N_H(x, y) = G^T\left(t = t_c^-\right) \cdot \sum_{m \in \{2,4\}} A(x, y)_{*,m} \tag{E12}$$

$$N_C(x, y) = G^T\left(t = t_c^-\right) \cdot \sum_{j \in d, j \neq -1} y_j H(x, y)_{*,j} \tag{E13}$$

$$QALY(x, y) = G^T\left(t = t_c^-\right) \cdot H(x, y) \cdot \vec{1}, \tag{E14}$$

where $G^T\left(t = t_c^-\right)$ is a $1x25$ vector specifying the number of individuals in each transient state immediately before the treatment policy is initially applied:

$$G\left(t = t_c^-\right) = \begin{pmatrix} I_{0,-1}(t_c^-) \\ I_{1,-1}(t_c^-) \\ \vdots \\ ST_0(t_c^-) \\ \vdots \\ ST_4(t_c^-) \\ \vdots \\ IT_0(t_c^-) \\ \vdots \\ IT_4(t_c^-) \end{pmatrix} = \begin{pmatrix} l_{0,-1} \\ l_{1,-1} \\ \vdots \\ 0 \\ \vdots \\ 0 \\ \vdots \\ 0 \\ \vdots \\ 0 \end{pmatrix}, \tag{E15}$$

$A(x, y)$ is a $25x4$ matrix specifying the discounted probability of dying from non-HCV and HCVrelated deaths for non-treated and treated individuals, starting from each transient state. $H(x, y)$ is a $25x25$ matrix specifying the expected time spent in each transient state adjusted to the present value. Thus, yielding equations E16 and E17.

Considering disease progression in the utilities of both players, the discounted outcome for the PC is:

10.1 Extended population including injecting drug users

Due to transmission, elimination after mortality (related or unrelated to HCV) is not necessarily within reach. Thus, in typical health economics, the effectiveness of a possible policy is analyzed based on a fixed cohort in a finite horizon [83]. We consider the cohort as all individuals, infected and not infected, that were a part of the population until time t_d. Thus, no new cases are considered from this time on, but we continue following all individuals in the cohort throughout their lifetime. Therefore, we can model the process as a Markov model until the elimination of the cohort. Note, as a result of frequent checkups, individuals in the cohort may be treated also after time t_d.

Proposition *If no new HCV cases occur after time t_d, the total discounted number of individuals treated from time $t \geq t_c$ is given by:*

$$\begin{aligned} N_T(x, y) &= \sum_{i=0, i \geq j}^{3} \sum_{j=-1}^{3} x_j \sum_u I_{i,j}^u(t = t_c) \\ &+ \left(\sum_{k=1}^{t_d} \sum_{f=0}^{3} x_f \sum_{j=-1}^{f-1} y_j \cdot \sum_u I_{i,j}^u(t = t_c)(t_c + k\Delta t) \cdot \left(\frac{1}{1+r}\right)^{k\Delta t}\right) \\ &+ \mathcal{I}^T\left(x, t = t_d^+\right) \cdot \left(D(x, y)_{*,ST} + D(x, y)_{*,IT}\right) \cdot \left(\frac{1}{1+r}\right)^{t_d}, \end{aligned} \tag{E18}$$

where u denotes the injection behavior of individuals, i.e., active, IDU in HR, former or non-IDU. $\mathcal{I}^T\left(x, t = t_d^+\right)$ is the number of individuals in each transient state at time t_d and $\left(D(x, y)_{*,ST} + D(x, y)_{*,IT}\right)$ is a closed-form specifying the proportion of all individuals – IDU and non-IDU – who will be treated for HCV, adjusted to time t_d. Namely, the solution from time t_d is similar to the one presented in E11. Note as

$$U^{PC}(x, y) = p \cdot N_T(x, y) = p \cdot \left(\sum_{i=0, i \geq j}^{3} \sum_{j=-1}^{3} x_j I_{i,j}\left(t = t_c\right) + I^T\left(x, t = t_c + \Delta t\right) \cdot \left(B(x, y)_{*,ST} + B(x, y)_{*,IT}\right)\right), \tag{E16}$$

and the utility function of the country, $U^{COUNTRY}(x, y)$, is given by the following closed-form:

$$U^{COUNTRY}(x, y) = v \cdot G^T\left(t = t_c^-\right) \cdot H(x, y) \cdot \vec{1} - p \cdot N_T(x, y) - G^T\left(t = t_c^-\right) \left(\begin{cases} c_H \cdot \sum_{m \in \{2,4\}} A(x, y)_{*,m} + \\ c_C \cdot \sum_{j \in d, j \neq -1} y_j H(x, y)_{*,j} \end{cases}\right), \tag{E17}$$

the fixed cohort includes HCV and non-HCV infected individuals, the country's utility evaluation includes also the QALY of susceptible individuals.

Declarations

Ethics approval Not Applicable.

Consent to participate Not Applicable.

Consent for publication Not Applicable.

Conflicts of interest/Competing interests (include appropriate disclosures) The authors confirmed no conflict of interest.

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